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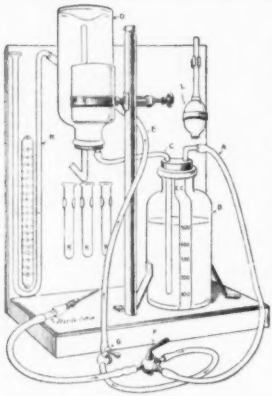

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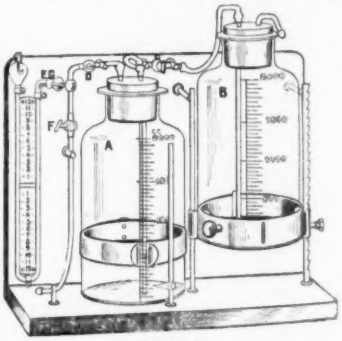

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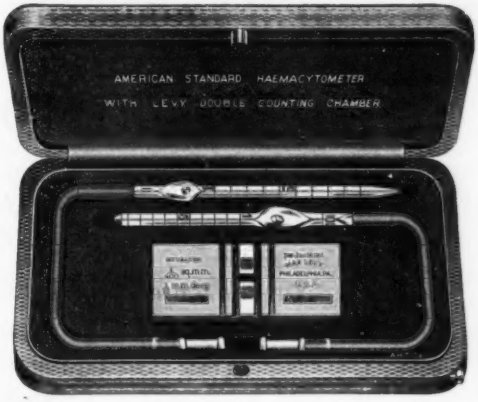

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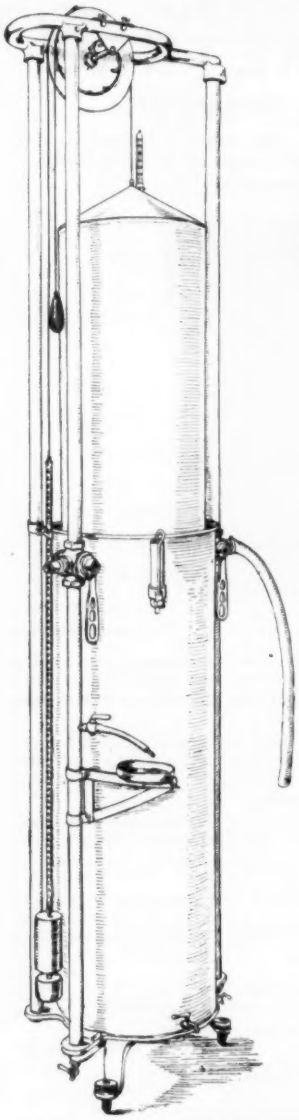

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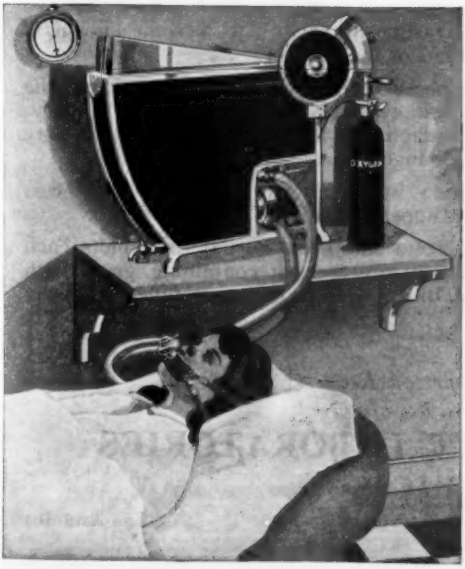

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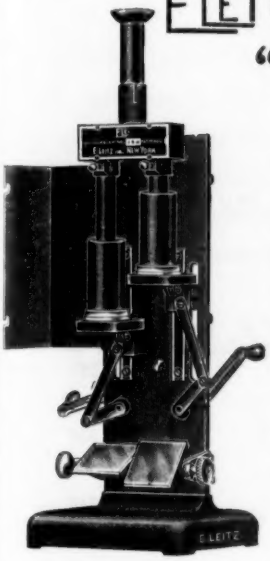

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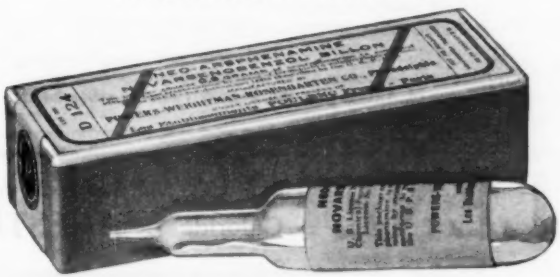

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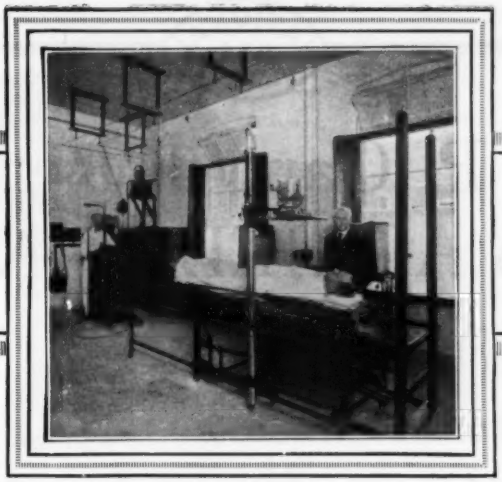

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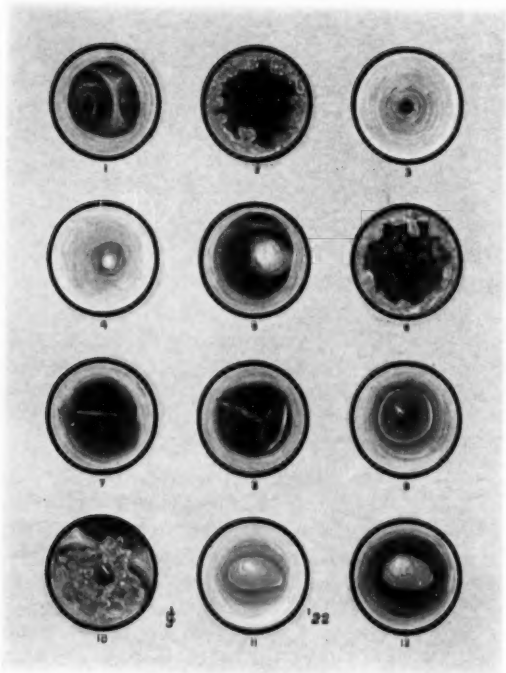

Bronchoscopic views.
(See page 317.)

THE

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MARCH, 1923

ORIGINAL ARTICLES.

THE MECHANISM OF PHYSICAL SIGNS, WITH ESPECIAL REFERENCE TO FOREIGN BODIES IN THE BRONCHI *.

By Chevalier Jackson, M.D.,

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It would seem interesting for me to illustrate for the internists present the bronchoscopic views of the most frequently seen departures from the normal in the interior of the bronchi. In other words to consider the changes in physical forms that must necessarily influence, according to the laws of physics, the physical signs as elicited by the internist examining through the barrier of the thoracic wall. At the outset it should be said that I am incompetent to elicit physical signs partly because while I have been endeavoring to train my eyes and fingers to the requirements of endoscopic technic, the training of my ears to the niceties of auscultation and percussion have been neglected. Fortunately, however, my patients and I have had the advantage of a number of the most skilled internists. Since roentgen-ray diagnosis of nonopaque foreign bodies in the lung by the discovery of Iglauer and its development to a high degree of perfection by my colleague, Willis F. Manges, it may be said that the roentgen ray is our most valuable means of diagnosis in all cases of suspected foreign body in the lung; but this does not lessen the necessity for the study of the physical signs. It would be a great misfortune if careful physical examination were neglected in any case. Every foreign

* Report of a "chalk talk" given at the meeting of the Section on General Medicine of the College of Physicians, February 27, 1922.

body case should be gone over as carefully as if the roentgen-ray had not been discovered and the signs should be recorded and interpreted *before* the roentgen-ray examination so the examiner will not be biased, or, as is often the case, hindered by his efforts not to be biased. It is so much easier simply to record "in cold blood" and interpret the findings as elicited with no knowledge of the ray-findings, that all of the internists with whom I have collaborated preferred to work that way.

Changeability of Physical Signs. One of the outstanding features of the physical signs, especially in foreign body cases, is their changeability, as pointed out by McCrae.[1] This changeability is well illustrated in all the bronchoscopic views except 1 and 7. The bronchial movements and the shifting of the secretions, the granulations and the foreign body all contribute to the changeability of the physical signs. The outstanding feature of all bronchoscopic endobronchial pictures is also the incessant change. The bronchoscopist without moving his bronchoscope from one location sees a never-ending panoramic series of changes from one image to another. The image is modified by:

(*a*) The bronchial movements.
(*b*) The presence, absence or shifting of secretions.
(*c*) The presence and movements of foreign bodies.

Necessarily in obedience to physical laws, the physical signs must in some degree change also. That they do thus change is abundantly evidenced by the clinical observations of the Bronchoscopic Clinic, a few of which are herewith illustrated.

The normal bronchial movements are probably not fully realized by anyone who has never looked through a bronchoscope into the normal living lung. It is an awe-inspiring sight. The bronchi are not rigid tubes like gas-pipes. They expand, contract, elongate, shorten; they bulge out, dinge in; bend and twist to an astonishing degree. Often the lumen of a normal bronchus proximal to a foreign body is noticed to be obliterated so as completely to hide a foreign body from view, simply by the momentary contraction of the normal walls of the bronchus. The same thing occurs from momentary bending and dinging in of the bronchial wall. These movements follow each other in rapid succession. They are rhythmically evident during respiration. Expansion and lengthening of a bronchus occurs during inspiration, contraction and shortening during expiration. These movements change the picture at the rate of 18 or more times per minute. They are enormously exaggerated during the expiratory blast of cough and the deep inspiration that immediately follows cough. The transmitted movements of the heart and great vessels change the picture at the pulsatory rate of seventy or more times per minute.

[1] Am. Jour. Med. Sci., 1920, **159**, 313.

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The Shifting of Secretions. Secretions, unless the bronchus is completely occluded (by a foreign body itself or by secretions, granulations, swollen mucosa, etc.) are constantly shifting. They go upward under the influence of the cilia, the "squeezing" of the contractile lung, the expiratory current, or the tussive blast. They may have a retrograde tendency, usually less marked, under the influence of gravity and of the inspiratory current. Speaking broadly, there is a tidal effect in the alternate accumulation of secretions and their tussive expulsion. They may be partially expelled and aspirated into the other lung, giving marked signs in the univaded side for a time at least.

Foreign Bodies in the Air Passages. Symptomatology and Diagnosis. *Initial symptoms* are choking, gagging, coughing, and wheezing, often followed by a symptomless interval. Foreign body may be in the larynx, trachea, bronchi, nasal chambers, nasopharynx, fauces, tonsil, pharynx, hypopharynx, esophagus, stomach, intestinal canal, or may have been passed by bowel, coughed out or spat out, with or without knowledge of patient. Initial choking may have escaped notice, or may have been forgotten.

Laryngeal Foreign Body. One or more of the following laryngeal symptoms may be present: Hoarseness, croupy cough, aphonia, odynphagia, hemoptysis, wheezing, dyspnea, cyanosis, apnea, subjective sensation of foreign body. Croupiness usually means subglottic swelling. Obstructive foreign body may be quickly fatal by laryngeal impaction on aspiration, or on abortive bechic expulsion. Lodgement of a non-obstructive foreign body may be followed by a symptomless interval. Direct laryngoscopy for diagnosis is indicated in every child having laryngeal diphtheria without faucial membrane. (No anesthetic, general or local, is required.) In the presence of laryngeal symptoms we should, I think, consider the following possibilities:

1. A foreign body in the larynx.
2. A foreign body loose or fixed on the trachea.
3. Digital efforts at removal.
4. Instrumentation.
5. Overflow of food into the larynx from esophageal obstruction due to foreign body.
6. Esophagotracheal fistula from ulceration set up by a foreign body in the esophagus, followed by leakage of food into the air-passages.
7. Laryngeal symptoms may persist from the trauma of a foreign body that has passed on into the deeper air or food passages or that has been coughed or spat out.
8. Laryngeal symptoms (hoarseness, croupiness, etc.) may be due to digital or instrumental efforts at removal of a foreign body that never was present.
9. Laryngeal symptoms may be due to acute or chronic laryn-

gitis, diphtheria, pertussis, infective laryngotracheitis, and many other diseases.

10. Deductive decisions are dangerous.

11. If the roentgen-ray is negative, laryngoscopy (direct in children, indirect in adults) without anesthesia, general or local, is the only way to make a laryngeal diagnosis.

12. Before doing a diagnostic laryngoscopy, preparations should be made for taking a swab-specimen and for bronchoscopy and esophagoscopy.

Tracheal Foreign Body. (1) "Audible slap;" (2) "palpatory thud," and (3) "asthmatoid wheeze" are pathognomonic. The "tracheal flutter" has been observed by McCrae. Cough, hoarseness, dyspnea and cyanosis are often present. Diagnosis is established by roentgen ray, auscultation, palpation, bronchoscopy. Listen long for "audible slap," best heard at open mouth during cough. The "asthmatoid wheeze" is heard with the ear or stethoscope bell (McCrae) at the patient's open mouth. History of initial choking, gagging, and wheezing is important if elicited, but is valueless negatively.

Bronchial Foreign Body. Initial symptoms are coughing, choking, asthmatoid wheeze, etc., noted above. There may be a history of these or of tooth extraction. At once, or after symptomless interval, cough, blood-streaked sputum, metallic taste, or special odor of foreign body may be noted. Non-obstructive metallic foreign bodies afford few symptoms and few signs for weeks or months. Obstructive foreign bodies cause atelectasis, drowned lung and eventually pulmonary abscess. Lobar pneumonia is an exceedingly rare sequel. Vegetable organic foreign bodies, such as peanut-kernels, beans, watermelon seeds, and the like cause at once violent laryngotracheobronchitis, with toxemia, cough and irregular fever, the gravity and severity being inversely to age of child. Bones and metallic bodies after months or years produce changes which cause chills, cough, foul expectoration, hemoptysis, in fact, all the symptoms of chronic pulmonary sepsis, abscess or bronchiectasis, and many signs which may suggest pulmonary tuberculosis. The apices, however, are normal and bacilli are absent from the sputum.

Physical Signs. The following is a brief *resume* of the results of the work of the various eminent internists who have collaborated with me: The physical signs vary in different cases and at different times in the same case. The results of my endoscopic studies of the mechanism of the production of the physical signs throw much light, I think, on the subject, as I shall now endeavor to show by a few drawings.* Secretions, normal and pathologic, may shift from one location to another; the foreign body may

* Reproduced in the color plate.

change position admitting more, less, or no air, or it may shift to a new location in the same lung or even in the other lung. A recently aspirated pin may produce no signs at all. The signs of diagnostic importance are chiefly those of partial or complete bronchial obstruction, though a nonobstructive foreign body, a pin for instance, may cause limited expansion (McCrae) or, rarely, a peculiar rale or a peculiar auscultatory sound. The most nearly characteristic physical signs are: (1) Limited expansion; (2) decreased vocal fremitus; (3) impaired percussion note; (4) diminished intensity of breath sounds distal to the foreign body. Complete obstruction of a bronchus followed by drowned lung adds absence of vocal resonance and vocal fremitus, thus often leading to an erroneous diagnosis of empyema. Varying grades of tympany are obtained over areas of obstructive or compensatory emphysema. With complete obstruction there may be tympany from collapsed lung for a time. Rales in case of complete obstruction are usually most intense on the uninvaded side. In partial obstruction they are most often found on the invaded side distal to the foreign body, especially posteriorly, and are often most intense at the site corresponding to that of the foreign body. A foreign body at the bifurcation of the trachea may give signs in both lungs. Early in a foreign body case, diminished expansion of one side, with dulness, may suggest pneumonia in the affected side; but the decreased vocal fremitus and the diminished breath-sounds with absence of, or decreased, vocal resonance, and absence of typical tubular breathing, should soon exclude this diagnosis. Bronchial obstruction in pneumonia is exceedingly rare.

Description of the Color Plate. Reference to the color plate reproduction of the chalk drawings along with the following notes of the outstanding features of the physical signs in the corresponding cases will doubtless be of interest. To avoid confusion all signs that seemed without special significance will be omitted. By this, however, it is not meant that the signs are due to the conditions illustrated, as, of course, it is impossible to say. The clinical facts are recorded for what they may be worth. Unless otherwise mentioned the physical signs noted corresponded to the tributary area of lung.

1. Bronchoscopic view looking down the right main bronchus of the living patient. The bronchoscopic tube-mouth is at the orifice of the main bronchus. The author's belief is that the normal breath sounds are largely produced by the impinging of the air-blast on the thin sharp edges of the spurs between the branch orifices. The view is somewhat composite, inasmuch as the bechic, respiratory, pulsatory and bronchial movements prevent a simultaneous view of all the branch-bronchial orifices shown, as mentioned in the paragraph on bronchial movements.

2. View looking down the right main bronchus in a case of post-

pneumonic pulmonary abscess. The walls of the bronchus are lined with exuberant granulations which have also obliterated the normal thin, sharp dividing spurs seen in illustration 1. Obviously, by the laws of physics, air rushing through such a tube must give an auscultatory sound different from the passage of air through a normally lined tube and impinging on sharp dividing spurs, as shown in the preceding illustration. A brass horn lined with obstructing masses of grease and incrustations would give a note perceptibly different to sensitive ears, from that obtained from a clean, polished, unobstructed horn. The difficulties encountered at the Bronchoscopic Clinic in designating a peculiar sound as characteristic of this state of a bronchial tube is due to the almost invariable association with pus produced by the granulations. The granulations shown at 2 are often seen to flap to and fro in the respiratory current or bechic blast. They are quite often associated with the conditions shown at 5 and 6, though the latter represent other cases. Coughing up the purulent secretions may in a few moments restore the condition shown at 2. Dr. O. H. Perry Pepper elicited the following signs: Limited expansion; dulness at base; expiration prolonged and of bronchial quality; breath sounds absent at base; vocal resonance unaltered; no whispered pectoriloquy.

3. Arachidic bronchitis, due to aspiration of a peanut-kernel which does not show. The bronchial mucosa has swollen until only a small lumen remains. For convenience this is called a pin-hole lumen, though it may be considerably larger than a pin-hole. The outstanding physical signs in this case before bronchoscopy were: Limited expansion on the invaded side, diminished, sometimes absent, breath sounds, impaired percussion note and occasionally a long, wheezing expiratory rale, alternating with absence of rales.

4. Same case as shown at 3, a few moments later. The pin-hole lumen has been occluded with a thick, firm clot of pus which was removed with forceps. Although no physical examination was made at the moment this bronchoscopic image was seen, the inference is logical that the intermittent disappearance of all breath sounds corresponded with an intermittent occlusion of the lumen similar to that noted at bronchoscopy and shown in this and the preceding illustration.

5. Pus coming into the right main bronchus from the upper-lobe bronchus (recumbent patient); partial occlusion of the right main bronchus. A few moments later the pus was aspirated into the orifice of the middle-lobe bronchus which is here shown anteriorly (above and beyond the pus in the drawing). Physical signs: Limited expansion and coarse rales all over right side; intermittent diminution of breath sounds over middle lobe; impaired percussion note right upper lobe.

7. A slender bit of steel (shaft of a dental instrument) transfixed across the lumen of the left stem bronchus. The logical hope would

be that some peculiar eolian note might be heard from the air-blast rushing past the slender wire. Nothing of the kind could be made out. Instead a most illogical and so far unexplained phenomenon was observed in this case by Dr. McCrae; namely, a limitation of expansion on the invaded side. In consideration of the fact that there was, as clearly shown at bronchoscopy and illustrated here, no obstruction to the airway, this curious, phenomenon is difficult to explain. Since this case the same thing has been noted in a great many similar cases. The only other sign of note was the presence of fine "tissue-paper" rales. Both these and the limitation of expansion disappeared after bronchoscopic removal of the foreign body.

8. A tack in the right stem bronchus. In this position there is a partial by-passage of air. Physical signs were limitation of expansion, impaired percussion note, diminished breath sounds and coarse rales. In the case of a piece of bone in this same location, Dr. Stengel localized the bone by exaggerated harsh breath sounds having their maximum intensity posteriorly corresponding to the endobronchial location from which I subsequently removed the foreign body with the bronchoscope.

9. This tack, because of the position of its head, completely occludes the bronchus. Physical signs: Limitation of expansion, absence of breath sounds, flat percussion note, absence of rales on the invaded side, loud rales in great variety in the other lung. Illustrations 8 and 9 show different cases of the same kind of tack, of which nearly two dozen have come to the Bronchoscopic Clinic. In a number of these cases I have noticed at bronchoscopy the tack shifting from a position similar to that shown at 8 to a position similar to that shown at 9. It is logical to suppose that a similar shifting occurs to account for the changeability of the signs so often noted in this kind of foreign body and, in fact, in almost all kinds of foreign bodies.

10. A tack in the lower-lobe bronchus, embedded, because of its prolonged sojourn, in a mass of soft, flabby, exuberant granulations which are partially occluding the orifice of the middle-lobe bronchus. Before the bronchoscopy Dr. McCrae had noticed intermittently a diminution of breath sounds over the middle lobe. The natural inference is that there were intermittent and varying degrees of obstruction of the middle-lobe bronchus because of the location of the tack, the granulations and the pus at its orifice. The physical signs were: Limitation of expansion, a flat percussion note and absence of rales and breath sounds over the right lower lobe; a flat percussion note and absence of rales and breath sounds over the right lower lobe; a variety of rales and, intermittently, diminished breath sounds over the middle lobe; coarse rales at times in the other lung. In a number of similar cases a rib resection has been done under a mistaken diagnosis of empyema.

11. A peanut-kernel in the right bronchial orifice almost completely occluding the bronchus *during expiration only.*

12. The same patient as in illustration 11; view a moment later, at the *beginning of inspiration.* The "forceps spaces" have opened up for the inspiratory by-passage of air, the exit of which is impeded by the collapse of the bronchial wall shown in the preceding illustration. This is the explanation, afforded by bronchoscopy, of the most important diagnostic phenomenon of obstructive emphysema, discovered by Iglauer and developed to a high degree of certainty by Manges.

THE NATURE OF THE COMPLEMENT FIXATION REACTION IN SYPHILIS IN RELATION TO THE STANDARDIZATION OF TECHNIC.*

By John A. Kolmer, M.D.,

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(From the Dermatological Research Institute of Philadelphia and the Department of Pathology and Bacteriology of the Graduate School of Medicine of the University of Pennsylvania.)

The literature upon the Wassermann and other serum reactions in syphilis has become so voluminous and the subject has been discussed so frequently and with such detail, that it would appear almost superfluous to devote more time to it. On the other hand, syphilis is so widespread and of such high economic importance, is so likely to be encountered in every specialty of medical practice, and may so easily escape clinical detection in certain stages, that the subject is one of universal interest and great importance, and improvements in our aids to diagnosis are to be welcomed. No other strictly laboratory test has been more used and abused, lauded and condemned and frequently misunderstood than the Wassermann test; yet its intrinsic worth has enabled it to weather all storms so that it probably stands today, potentially at least, the most important single laboratory procedure, full of possibilities for great good when properly conducted and interpreted, but of even greater possibilities of harm when technically incorrect and misunderstood.

The Proper Function of the Complement Fixation Reaction in Syphilis. Syphilis in its first and especially in its later manifestations may so readily engage attention in every specialty in medicine that all physicians must expect to encounter it in their practice. Specialists are usually highly skilled in detecting the disease when it involves

* Read by invitation before the New York Academy of Medicine, December 20, 1921.

their particular domain of work, but in its later stages with varied clinical manifestations the disease may easily escape detection by the general practitioner. In its latent stages it may escape diagnosis by even the most skilled physician, as likewise the atypical case with a negative or indefinite history. The complement fixation test in order properly to fulfill its function must prove of most aid under these conditions—not to replace clinical acumen and judgment, but to furnish an additional and accurate means of diagnosis of the clinically difficult, doubtful or unsuspected case. When and where clinical skill is least, reliability of the serum test should be greatest, and for this reason the technic is deserving of more attention as part of the nation-wide movement for the diagnosis and thorough treatment of syphilis.

Probably with the majority of physicians the Wassermann test is acceptable only as confirmatory evidence of syphilis. Many are unwilling to ascribe any significance to the reaction in either a positive or negative way unless the result meets with their clinical expectancy. Doubtless not a few have been forced into this attitude by actual experience. I believe, however, that it is possible to avoid technical errors and greatly improve the diagnostic status of the test, and that it should be the aim and purpose of serologists to evolve a test capable of correctly detecting the disease when this is not possible by clinical means; to me the complement fixation tests fails in its ultimate mission and purpose if it fails to do so. I believe that falsely positive reactions are most likely to be caused by technical errors, and that, as in other branches of medicine, skill and experience are required to reduce their incidence to a minimum. I believe that with improved technic the incidence of falsely positive reactions will be negligible because there is no biological reason for their occurrence in any nonsyphilitic disease other than frambesia tropica. Falsely negative reactions, however, will probably always occur for biological reasons, because no matter how sensitive a test may be made it cannot detect in the serum or spinal fluid something that is practically absent, and it would appear that in some cases of latent syphilis the activity of spirochetes is so slight or their numbers and virulence so reduced, that demonstrable amounts of "reagin" are not produced.

I trust that this high ideal of the complement fixation test in syphilis is justifiable. According to my own observations and experiences I believe it is, although I admit that the full possibilities of the test are realized only by close coöperation between clinician and serologist or by him who possesses training and experience in both branches.

Nature of the Complement Fixation Reaction in Syphilis. The complement fixation reaction occupies a very unique position among immunological phenomena. At first regarded as a specific reaction, it is now known to be biologically non-specific, but in most parts

of the world this does not seriously reduce its diagnostic value in syphilis because the peculiar antibody-like substance to be found in the blood or spinal fluid or both, and responsible for the reaction, is known definitely to occur only in syphilis and frambesia tropica, or yaws.

Infection with spirochetes of these two diseases results in the elaboration of a substance aptly called "reagin" by Neisser, which has the property of uniting or reacting with certain lipoidal substances, the resulting complex regarded as a precipitate by some investigators, being able to absorb or fix hemolytic complement in the test tube. This "reagin" is probably produced by the cells directly in contact with and stimulated by the spirochetes; it is first found therefore in the tissue juices of the chancre, as recently shown by Klauder and myself. As the spirochetes are disseminated through the body the tissues of various internal organs, including those of the brain and spinal cord, very probably participate in the production of this Wassermann substance or "reagin." Even the cells of the cardiovascular system may participate in the process as likewise the lymphocytes and other cells of inflammatory stimulation surrounding the nests of spirochetes. It may be that the lipoids of spirochetes are antigenic and induce the production of the "reagin," but so far all attempts to produce antibodies with pure lipoids have failed, and even if it were true, one would expect a certain degree of specificity on the part of these lipoids which has not been demonstrated. This view does not coincide with our present conception of the tissues usually concerned in antibody production in infectious diseases, but there are no valid reasons for regarding this cellular "reagin" as a true antibody. In the first place the amount to be found in the body fluids bears a more or less direct relation to the severity of infection, although this relation may not be clinically apparent if the spirochetes are active in tissues of minor physiological importance. In the second place it may be present during the latent or resting stages of the disease in such small amounts as to escape detection, whereas if it were a true antibody capable of forcing the spirochetes into these periods of latency, it should be demonstrable in large amounts. For these and other reasons the complement fixation reaction is to be regarded as an index of the degree of infection rather than of immunity, and if this is true the phenomenon is unique, not only for this reason but likewise because of the peculiar nature of the "reagin."

This "reagin" has the power of fixing complement in the presence of a suitable suspension of lipoids. It is probably not itself a lipoid or identified with the lipoid content of serum or spinal fluid, although this phase of the subject is by no means a closed chapter and requires further investigation.

The Practical Specificity of the Complement Fixation Reaction in Syphilis. The important practical question is—May similar

cellular "reagins" be produced in diseases other than syphilis and frambesia, capable of bringing about the physico-chemical phenomenon of complement fixation in the presence of extracts of lipoids? Do the positive Wassermann reactions which have been recorded as occurring in leprosy, diabetes mellitus, during the febrile stages of malaria, typhoid fever, pneumonia, late pregnancy, and so on, answer the question affirmatively? When one remembers the many chances of technical error capable of involving every important element and phase of the test, the answer must be given with great caution. Furthermore, may not pregnancy, an intercurrent infection, a metabolic disease and so on, stimulate latent foci of syphilitic spirochetes into activity with the production of "reagin," just as trauma may possibly be provocative or stimulating?[1] I am sure that this question of non-specific reactions cannot be answered by a mere review of the literature upon the Wassermann reaction in nonsyphilitic diseases because too much of it has been built upon obvious technical errors. Neither do I disclaim the possibility of observing positive complement fixation reactions with a correct and acceptable technic in nonsyphilitic diseases, but I do know that the clinician is not always infallible in his judgment that syphilis can escape clinical detection and that these unexpected positive reactions are not always due to laboratory error. My question remains—Is a "reagin" similar to that produced in syphilis and frambesia, or a physico-chemical alteration of the blood and spinal fluid similar to that occurring in these diseases, to be found in other infectious and non-infectious diseases? A final answer cannot be given, as the subject requires further investigation; but if I may be permitted to express a prediction, I believe that the answer will be negative and that as clinical and pathological knowledge of syphilis is developed and more especially as our complement fixation technic is perfected, more and more emphasis will be placed upon what may be called the "syphilitic significance" of these unexpected and weakly positive reactions with the sera of individuals regarded tentatively as nonsyphilitic.

A source of clinical error worthy of keeping in mind is that a positive Wassermann reaction does not necessarily mean that a particular lesion is syphilitic; for example, a tuberculous ulcer may occur in the larynx of an individual with latent syphilis and fail to improve with antiluetic treatment. On the other hand the complement fixation reaction may yield falsely negative reactions, and not a few physicians regard the test as insufficiently sensitive.

Biologically Falsely Negative Reactions and the Necessity for a Sensitive Test. These false reactions may be due to the presence of insufficient amounts of "reagin" in the blood or spinal fluid or

[1] A recent paper by Klauder on Syphilis and Trauma (Jour. Am. Med. Assn., 1922, **78**, 1029) is very instructive in this connection and answers this question affirmatively.

to technical errors. The mere fact that a person is known to have contracted syphilis does not necessarily mean that the "reagin" is present in detectable amounts. There must be a certain degree of spirochetic activity and doubtless numbers of spirochetes, their virulence and location in the body are important modifying factors. Warthin has shown that spirochetes may exist in the tissues with practically no inflammatory reaction and under these conditions "reagin" production must be very slight.

Therefore the technic of the complement fixation reaction in syphilis should be as sensitive *as is possible with specificity*. Every serologist knows that the test may be rendered so delicate as to incur the risk of non-specific reactions, but the harmfulness of these is so apparent that they are not included in the present discussion. Whether or not cases of latent syphilis unexpectedly detected by the complement fixation reaction are subjects for mild, moderate or intensive treatment is likewise aside from the present discussion. There ought to be, however, no difference of opinion of the desirability of having a complement fixation test as sensitive as is possible with practical specificity in order to avoid falsely negative reactions and especially when the test is employed as a guide to treatment to avoid the regrettable error of undertreating the disease. Even under these conditions we will continue to secure falsely negative reactions for the very good biological reason that where "reagin" is practically absent from the serum and spinal fluid it cannot be detected in the test tube. In connection with this subject of biologically falsely negative Wassermann reactions it is worthy of remembering that while "reagin" may not be present in detectable amounts in the blood, sufficient may be present in the spinal fluid for yielding positive reactions. The reason is unknown. It may be that in these cases the spirochetes are mainly located in the tissues of the brain and spinal cord and that the "reagin" produced by these tissues finds its way into the spinal fluid where it may be detected in smaller amounts than is possible in the serum because five to ten times more spinal fluid may be employed in the Wassermann test than is permissible with serum. I believe this to be the principal reason, but in addition it may be that some of the "reagin" is filtered out of the spinal fluid during its reabsorption into the lymphatic and vascular systems.

Studies in the Standardization of Technic. During the past six years my colleagues and myself[2] have been actively interested and engaged in a series of investigations aiming to study every phase of complement fixation in syphilis for the purpose of building up a test possessing a maximum degree of sensitiveness with the minimum possibility for yielding non-specific reactions. I realized

[2] Series of thirty-two papers being published in the Am. Jour Syph., beginning 1919, **3**, 1.

that the task was big before a start was made, but did not conceive that it would require the very large amount of work that has been done. As our investigations proceeded it became evident that every detail, regardless of how trivial it may at first appear, was worthy of careful study. My associates and myself have striven always to conduct the work without preconceived ideas and without bias. It can scarcely be hoped or expected that we have escaped technical errors and erroneous conclusions, but we have faithfully described what we have done and what we have observed. These investigations have finally enabled us to build up a new complement fixation test for syphilis which I hope others will find as satisfactory as ourselves and that clinicians and serologists will at least consent to give it a fair trial alongside of their own technic.

Standardization of the complement fixation reaction has been discussed and if accomplished may yield certain advantages. For example, it would enable a closer analysis and evaluation of different kinds and methods of treatment and greatly increase the confidence of the medical profession as a whole in the test as an aid in the diagnosis of syphilis.

Doubtless many physicians have had the unhappy experience of securing varying reports on the Wassermann reaction with portions of the same blood sent to different laboratories. This is regrettable but not altogether unexpected, when one remembers the great influence of technic upon the reactions and the numerous modifications being practised. Standardization of technic would aim to correct this situation, but it is easy to fall into the error of making the "remedy worse than the disease." For example, if it were desired to simply unify the results insofar as positive or negative reactions were concerned, a simple modification of the original Wassermann reaction could be made to fulfill the requirement. In other words by adopting a technic capable of detecting only relatively large amounts of "reagin" the weakly positive or doubtful cases which constitute those giving varying results would be weeded out by giving negative reactions. Only gross technical errors would interfere with uniform results under these conditions, but is such a reaction worth while? Are not the truly syphilitic cases in the latent stages worthy of detection even though antiluetic treatment may not be given? Should not a reasonable attempt be made to make treatment as thorough as possible? When treatment is being guided by the complement fixation reaction, should not the test be made as sensitive as is possible with practical specificity in order that a truly positive reaction may be the last symptom to disappear and the first to return if complete sterilization has not been accomplished?

I have not called our new test a standardized test because it must earn that designation by common consent. But experience with it has been favorable, and I am hoping that it may, at least,

prove a starting-point toward the adoption of a standardized technic. A new antigen and many technical improvements have been included to give the technic five qualifications as follows: (1) As high degree of sensitiveness as is permissible with practical specificity; (2) technical accuracy and uniformity in results insofar at least as positive or negative reactions are concerned. Slight variation in the degree of positiveness will occur, but these do no harm as long as the primary question of whether a serum does or does not yield a positive or negative reaction is answered; (3) to yield a truly quantitative reaction in order to give an index of spirochetic activity and the influence of treatment; (4) to be technically simple in order to reduce the minimum of error, and (5) economical of time and materials insofar as this is consistent with the best work. Simplicity is but a relative term; for the inexperienced any technic is apt to be complicated, but for the experienced my new test is simple. It is not a short-cut method and has never aimed to be, because too many sources of error require attention and correction to fulfil the primary aim of sensitiveness and specificity.

The new complement fixation test for syphilis has aimed to meet these requirements as follows, a fuller discussion and all technical details being given elsewhere:[3]

I. *The requirement of sensitiveness* by the following procedures:

(*a*) By using a highly sensitive antigen.
(*b*) By using relatively large amounts of antigen.
(*c*) By using relatively large amounts of serum and spinal fluid.
(*d*) By heating sera for only fifteen minutes at 55° C. instead of for thirty minutes.
(*e*) By using a mixture of guinea-pig complements prepared in a manner tending to increase sensitiveness to fixation.
(*f*) By mixing serum and antigen for a brief period before the addition of complement.
(*g*) By using a primary incubation of fifteen to eighteen hours in a refrigerator at 6° to 8° C. plus ten minutes in a water-bath.
(*h*) By close adjustment of the hemolytic system.
(*i*) By using an antisheep or antiox hemolytic system, although the test can be conducted with an antihuman system.
(*j*) By reading the reactions within three hours after the conclusion of the secondary incubation.

[3] Kolmer, J. A.: Am. Jour. Syph., 1922, **6**, 82.

II. *The requirement of practical specificity by:*
   (*a*) Close adjustment of the hemolytic system to a primary incubation of fifteen to eighteen hours at 6° to 8° C.
   (*b*) Careful titration of antigen under conditions rendering the dose employed suitable for this kind of primary incubation.
   (*c*) Including numerous and adequate controls.

III. *The requirement of technical accuracy and uniformity in results by:*
   (*a*) Adopting the principle that pipetting relatively large amounts of fluid (0.2 to 1 cc) tends to greater accuracy than measuring smaller amounts (less than 0.2 cc).
   (*b*) Using a total volume of 3 cc with sufficient corpuscles and test-tubes of suitable size to yield clear, sharp, and easily read reactions.
   (*c*) By using a reading scale prepared each time the tests are conducted and with the same reagents.

IV. *The requirement of a true quantitative reaction*, so important in connection with the use of the complement fixation test as a guide and control in treatment, has been met by working out a series of five dilutions of patient's serum and spinal fluid which may be set up rapidly and accurately.

V. *The requirement of simplicity* has been met insofar as experienced serologists are concerned. Simplicity is but a relative term, inasmuch as the simplest technic is a complicated problem for the inexperienced and insufficiently trained worker, whereas a more complicated technic is perfectly simple to the experienced serologist. I am quite sure that my new test can be satisfactorily conducted by any person possessing a working knowledge of the technic of complement fixation.

VI. *The requirement of economy* has been met insofar as materials are concerned; in regard to time the new test is not a short-cut method and is not shorter than other methods in general use.

A few lines may be added on the subject of uniformity in results: It must be emphasized that the anticomplementary activity of serum or spinal fluid is very important in relation to reactions, and for this reason tests conducted with portions of the same specimen of blood in different cities cannot be expected to yield absolutely similar results, nor even in the same city, if serologists vary in their methods of preserving blood until the tests are conducted.

Two or more serologists working in the same or different laboratories testing portions of a sample of blood or spinal fluid from

one person should agree at least upon the question of positive or negative reactions; in my experience most variation occurs with sera yielding weakly positive or borderline reactions. Slight discrepancies in the reports on the degree of complement fixation must be expected, inasmuch as the personal equation plays an important part in reading the degree of hemolysis, as it does in matching colors in other lines of work. Slight discrepancies of this kind do no harm as long as the primary and fundamental question of whether a serum does or does not yield a positive or negative reaction is untouched, and particularly with sera yielding borderline results.

Is Standardization Advisable and Possible? Standardization is desirable if these aims are served and satisfied: The first purpose should be to secure as good a technic as is possible to evolve in the light of our present knowledge. Mere unification of results in Wassermann tests in different laboratories means little or nothing unless the test is technically correct and as sensitive as is possible with practical specificity. Even under these conditions individual variation in the scientific attainments and accuracy of different serologists will ever be modifying factors, if the test aims to be a sensitive one; but I believe standardization is possible under these conditions, and my own efforts have been and will continue to be dedicated to that end.

THE PRODUCTION OF HEART MURMURS.*

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The detection and study of murmurs if present form perhaps the most important feature of cardiac auscultation. That not all murmurs indicate disease of the heart has long been recognized, but it is often difficult to decide as to the interpretation to be placed on a given murmur. The recent emphasis laid on the relative unimportance of a systolic murmur heard over the cardiac apex has given the matter a renewed interest. To interpret correctly heart murmurs an understanding of the chief facts pertaining to the production of murmurs would seem to be essential. It is the purpose of this paper, therefore, to discuss in part the literature on the subject and then to present the results of a few simple experiments and clinico-pathologic observations.

Literature. Laennec,[1] the father of auscultation, explained murmurs as due to a spasmodic contraction of the heart or arteries.

* Read in part before the Harvard Medical School Research Club, February 24, 1922.

[1] Traité de l'auscultation mediate, 1826, **2**, 441.

His main proof of this conception was that postmortem examination failed to disclose any constant findings and that often the heart was found to be structurally normal. That spasm could not be the cause of heart murmurs was clearly shown by Corrigan, the Dublin physician whose name is still linked with the collapsing or water-hammer pulse of aortic regurgitation. Corrigan subjected the matter to experiment, using a length of small intestine attached to a water pipe from which a stream of water was allowed to pass through the piece of bowel. As a result of his observations he attributed the causation of murmurs to the formation of a jet. Thus he wrote: "When an artery is pressed upon . . . the action of blood in the artery immediately beyond the constricted part (looking from the heart) is no longer as before. A small stream is now rushing from a narrow orifice into a wider tube and continuing its way through the surrounding fluid."[2] And in a later paper appeared his conception of the action of this jet as follows: ". . . its particles tending to leave vacuums between them throw the sides of the tube into vibration, which can be very distinctly felt by the finger and which gives to the ear the peculiar sound *bruit de soufflet* and to the touch *fremmissement*."[3]

Corrigan's ideas were the subject of much controversy, and it was not until 1858 that Chauveau, of Lyons, placed the question of murmurs on a sound basis. This French physiologist and veterinarian carried out a large series of observations, mostly on horses, in which a considerable length of the carotid artery or jugular vein was easily exposed by surgical means and subjected to experiment. Chauveau's work was so carefully done, and so many of his conclusions appear correct even today, that it seems worth while to repeat the latter here. The details of the experiments on which he based his statements may, for the most, part be omitted, as to include them would unduly lengthen this paper. The observations of this clear-headed scientist[4] are, then:

1. Vascular murmurs do not depend directly upon the quantity or the quality of the blood which is circulating in the vessels.

2. The asperities which roughen the internal surface of the circulatory tubes, without modifying the caliber of the latter, cannot be a cause of a murmur.

3. When a dilatation exists in the course of a vessel, the blood, on arriving at this dilated part may produce a murmur.

4. Narrowing of the vessels may cause a murmur, but the latter is not due to the entry of the blood into the narrowed part or through it. . . . The murmur occurs just beyond.

5. A dilatation is necessary, but also (*a*) sufficient dilatation and (*b*) a certain force to the blood stream.

[2] Corrigan, D. J.: Lancet, 1828, **2**, 4.
[3] Corrigan, D. J.: Edin. Med. and Surg. Jour., 1832, **37**, 225.
[4] Chauveau, M. A.: Gaz. méd. de Paris, 3me Série, 1858, **13**, 247. The translation adheres to the author's words as far as is consistent with good English.

6. Although it is true that there is necessary a certain difference in diameter between the dilatation where the murmur takes place and the narrowing, real or relative, which precedes this, so that the murmur is manifest, it does not follow that the more pronounced the difference the greater the intensity of the sound produced. When the entrance to the dilated part becomes very small and permits the passage of only a very small thread of blood, the murmur though remaining distinct, rough even, loses much of its intensity, the more so as the thread of blood is the less voluminous. It is when the blood arrives as a large wave in a large cavity that one is more likely to observe a strong murmur.

7. The pressure must be at least one-quarter of that in the left ventricle (in the horse 5 cm. column of mercury). If this pressure is increased the intensity of the murmur increases proportionately.

8. The murmur is propagated along the vessel beyond and on the near side of the point of production (farther if more intense) but always farther with the blood stream. On the near side it has the sound of a file cutting on iron, and beyond, with the stream, that of the rasp of wood being sawn.

9. Like all possible sounds the immediate cause of murmurs are molecular vibrations.

10. In anemia the lessening of the number of cells is accompanied by a lessening of the blood volume. This diminution, while lowering the pressure exerted during diastole on the semilunar valves, greatly increases the force of the impulsion which animates the blood when it is driven into the arterial system. This force of impulsion is further increased, often, by the greater energy which the heart-beats acquire in anemia.

11. The essential stethoscopic sign of anemia is a cardiac murmur synchronous with ventricular systole.

12. Anemia does not cause arterial murmurs, but one can produce them by pressure, perhaps, a little easier than in healthy adults.

13. In anemia murmurs may be heard in the veins of the neck, as here only does one find the conditions which cause a *veine fluide*,[5] the cause of a murmur.

It will be noted that Chauveau is quoted as asserting that "the asperities which roughen the internal surface of the circulatory tubes, without modifying the caliber of the latter, cannot be a cause of a murmur." This is a contradiction of the observation of Theodor Weber,[6] who, in 1854, reported that roughness of the internal surface of the vessel caused a murmur.

About ten years later, in 1868, appeared an important monograph

[5] This term, originating in the French, is now freely used by English writers. Perhaps the word jet is a good translation.

[6] De Causis Strepituum in Vasis Sanguiferis, Leipzig, 1854, p. 8.

by Bergeon[7] on the production of murmurs. This author accepts the principles established by his predecessor, Chauveau, to whom he courteously gives full credit, and adds some further points. Of these there are two which take preëminence.

1. The *veine fluide* is a secondary phenomenon, just as are the rings in a mill pond into which a stone has been dropped. The phenomena of compression and reaction, which take place as a fluid under pressure passes by a spot where there is a sudden change in the caliber of the vessel, constitute the primary disturbance or shock (*l'ébranlement*). Perhaps this will be a little clearer if I quote a few sentences: "As all the molecules cannot pass the constriction at the same time, some will be crowded back and compressed. These latter, as a result, acquire a greater tension and in their turn go out, at the same time compressing and crowding back others, etc. From this results a series of alternating motions of equal intervals and in close succession."[8] This is Bergeon's explanation of the vibrations in the *veine fluide*, and it is these vibrations, he asserts, which produce the murmur.

2. The phenomena of compression and reaction also occur when there exists a cul-de-sac against the current and the murmur occurring under this condition is propagated up stream. Bergeon finds the occurrence of the cul-de-sac analogous to the bevel which is found in the mouthpiece of a flute.

Some lesser points concerning the production of murmurs are described by the same author. Thus the murmur was unaffected by the composition of the narrow area. Tests were made with copper, glass, porcelain, gutta-percha and rubber. Also the thickness of the wall at the constricted area was without influence. As regards the viscosity of the fluid flowing through the tubes, Bergeon agreed with Potain[9] that it modifies the murmur by its effect on the speed of the current; but he also satisfied himself by experiment that it influences the manner of vibration of the liquid. A musical quality of the murmur was found to result from impinging of a thin piece of membrane in the trajectory of the *veine fluide*. Bergeon quotes instances in which postmortem examination had disclosed some fibrous pathological formation[10] which had so influenced the character of the murmur. The jet, or *veine fluide*, it is to be remembered, had already been produced by a sudden narrowing of the lumen of the vascular tube. Murmurs are modified in transmission at times. Thus a metallic quality has been found to be associated with the resonating effect of some cavity, as the stomach distended by gas, a suitably located cavity in the lung, and in pneumothorax.

[7] Des causes et du mechanism du bruit de souffle, Adrien Delahaye, Libraire-Editeur, Paris, 1868.

[8] Idem, p. 79.

[9] Compt. rend. de la Gazette d. hôp., May 28, 1867, p. 252.

[10] Not mere roughening.

The conditions attending the presence of murmurs are again considered in 1881 by the French physiologist Marey. In a rather tiresome chapter[11] this author advances the theory that a sudden change in the blood-pressure is the essential condition in the production of a murmur. Of course that is just what occurs, according to physical laws,[7] on either side of a narrowing sufficient to cause some obstruction to the passage of the blood stream. A little thought makes it evident that Marey's experiment in raising and lowering the pressure in a tube just beyond a constricted area may more properly be considered as merely influencing the speed of the flow past the narrowing. It seems like putting the cart before the horse to attribute to the alteration in the blood-pressure on either side of a narrowing of the lumen the primary cause of a murmur. Marey, with his attention centered on alterations in blood-pressure as the real cause of murmurs, helps us, however, by pointing out that where the arterial tension is lowered by peripheral dilatation (relaxation of the arterioles) the occurrence of murmurs is favored. Fever is cited as an example. Perhaps this is one of the factors influencing the frequent occurrence at the aortic area of a systolic murmur along with the diastolic in those cases of aortic regurgitation in which there is a well-marked Corrigan pulse (a lowering of the diastolic pressure is characteristic).

Davison calls attention to the sound produced if the *veine fluide* strikes the surface of the bloodvessel. He writes: "When a membrane enclosing a liquid receives on its internal surface a stream which impinges on it, at any angle whatever, it will be thrown into sonorous vibrations, these vibrations giving rise to a sound when the stream impinges with rapidity and force, the pitch of which sound will depend upon the relative thinness of the membrane (the thinner the membrane the higher the pitch) and the intensity will depend upon the force of the stream, the vibrations giving rise to a soft blowing murmur when the stream impinges with little rapidity and force, and to a rough murmur when the rapidity and force are increased."[12] This, of course, is but an enlargement of certain observations previously made by Bergeon. It may be of help in explaining the greater transmission of murmurs with the course of the blood stream.

Geigel,[13] in 1893, concluded that murmurs are due solely to lateral vibrations of the vessel walls and sometimes of the valves. He admitted, however, that eddies, etc., occur at such places where murmurs are present; Heynsius made them visible by mixing powdered amber with the fluid. Geigel approved Weber's apt comparison of the blood with the bow of the violin and the vessel wall with the string.

[11] Marey, E. J.: Le Circulation du sang, Paris, 1881, p. 647.
[12] Davison, J. T. R.: Lancet, 1895, **1**, 1597.
[13] S. Virchow. Arch., 1895, **140**, 385.

Henri Soulier,[14] of Lyons, believes in the *veine fluide* but would add the murmur of the solid bodies (*souffles solidiens*), or, in other words, the murmur produced by the vibration of the valve involved. Soulier writes of the murmur down stream and up stream from the site of the narrowing, but these were both mentioned by Chauveau and Bergeon, while the latter described conditions (the cul-de-sac up stream) in which the murmur would both originate and be propagated up stream. Soulier points out that in mitral insufficiency the murmur heard in the back (especially if the transmission of that at the apex ceases in the axilla) may well be the murmur travelling down stream, *i. e.*, transmitted from the left auricle.

The explanation of the apex being the point of maximum audibility of the systolic murmur occurring in regurgitation through the mitral valve is commonly accepted as due to the fact that the apex is the part of the left ventricle which most closely approaches the chest wall. But, as Graham Steele points out, "the incompetent valves project backward into the blood stream, exactly like the lip or rim employed by Bergeon."[15] Thus the cul-de-sac against the stream exists (in addition to the narrowing through which the blood passes back to the left auricle) and if Bergeon's conclusions are sound there should be a murmur here and its transmission is up stream.

Thayer and MacCallum, in 1907, published an excellent paper[16] on the experimental production of murmurs in dogs. Their work and that of others demonstrate the ease with which murmurs may be produced artificially in animals.

Experimental. In the hope of obtaining a better understanding of the nature of murmurs detected in the physical examination of the patient, I have made some study of the murmurs which may be produced in rubber tubes through which a stream of water is passing. At first the work was done alone and consisted largely in the repetition of some of the simpler experiments of Gannet, Austin Flint and others, but finally realizing my ignorance of physics and the close connection of the latter with the problem of heart murmurs, I went to Prof. E. L. Chaffee, of Harvard University, for advice. Prof. Chaffee not only answered my questions but insisted on making some apparatus which enabled me to conduct experiments of greater reliability. It seems sufficient to merely summarize some of the tests and the results:

Rubber tubes, of pure rubber and of the caliber of 13 mm. and 7 mm. respectively, were connected with a number of appliances made of brass and representing various alterations in the caliber and contour of the vessel wall. The tube was auscultated above and below the appliance for the presence of a murmur as the water

[14] Lyon méd., 1899, **91**, 289.
[15] Med. Chronicle, Manchester, 1888, **8**, 105.
[16] Thayer, W. S., and MacCallum, W. G.: Am. Jour. Med. Sci., 1907, **133**, 256.

flowed through it. The fitting of the stethoscope with a short piece of rubber tubing, which had been burned to fit the curve of the tube through which the water was flowing, enabled one to auscult accurately without causing a stenosis by pressure of the end of the stethoscope in the effort to make an air-tight contact.

When the rubber tube is compressed with the fingers a murmur is readily produced. This is loudest just below the compressed area and is transmitted farther with the current than against. It varies in intensity with the velocity of the stream and the amount of the stenosis, but if the narrowing is progressively increased there is a point beyond which the maximum murmur is no longer audible. The accompanying diagrams (Diagram 1) show some of the conditions tested.

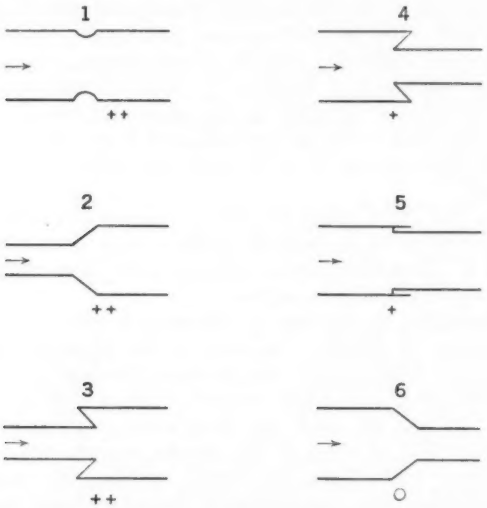

DIAGRAM I.—Cross-section of some of the conditions tested. The arrows indicate the direction of flow. ++ equals a good murmur. + is for a less intense murmur, O is used to signify an absence of murmur.

Figs. 1, 2 and 3 represent conditions favorable for the formation of a *veine fluide* or jet, and readily produced a murmur. Figs. 4 and 5 are examples of the cul-de-sac against the current, whose importance was emphasized by Bergeon. In the condition indicated by Fig. 5 there is merely a sharp lip where the rubber tube was passed over the end of a glass tube; there resulted a sharply localized murmur. In Fig. 6 there was essentially no murmur. The murmur was distinctly louder when associated with a condition which produces a *veine fluide*, as in Figs. 1, 2 and 3, and was heard better and transmitted farther down stream. The audibility and trans-

mission of the murmur in Figs. 4 and 5 was greater up stream. In all cases, as noted in the experiment of digital compression of the tube, a certain degree of velocity of the fluid was necessary and, within limits, the intensity of the murmur was proportional to the velocity of the circulating fluid.

Contrary to the observation of Bergeon it was found that the character of the murmur was influenced by the composition of the wall at the point where the murmur was produced. Thus there was a murmur where the stream of water from the faucet entered the rubber tube and the pitch of this became progressively higher as the auscultation was carried back to the faucet. In another instance the brass tube was connected to a glass tube with almost complete exclusion of the usual rubber tubing, and it was found that the murmur was weaker and of a different pitch.

The rubber tube was opened and for a distance of about two inches fine sand was stuck to its inner aspect by rubber cement. The slit in the vessel wall was then closed by rubber cement. When the water was turned on no murmur could be auscultated save one of very faint character when the stream was flowing at a high velocity. The tube was reopened and it was proved that the sand had not been washed away. In another experiment bits of the inner surface of the tube were cut out, leaving a surface definitely roughened by little pits with sharp edges averaging 1 to 2 mm. in depth and 3 to 4 mm. in greatest diameter. Result: no murmur could be detected.

It was found that when much sand or other material was made adherent to the inner wall of the tube a murmur was readily produced, but it is obvious that this was not a satisfactory test of the influence of roughness, as some degree of stenosis was then also present. It should be recalled that Chauveau cautioned against this error.

An experiment originally performed by Richard Geigel, to show the origin of the actual sound in the vessel wall, was repeated. A pail (Diagram II), was substituted for the glass beaker used by Geigel. In this experiment a murmur was present when the tube delivering the water practically impinged upon the bottom of the pail. A faint sound was detected when the tube was withdrawn so that the eddy around its mouth was made to play upon the bell of the stethoscope.

Clinico-pathologic. I have compared the clinical records and pathologic findings of the last 80 autopsies, all in 1921, at the Boston City Hospital. The group includes only cases which had been on one of the medical services, as there alone would one expect a careful record of the auscultatory findings. It is admitted that the records were written by interns who, of course, vary in skill, but it seems fair to believe that in the majority of instances the results of the physical examination were confirmed by the visiting physician. In

any case these records represent examinations of at least equal skill if not better than those of the average physician, and are confidently believed to be suitable for my purpose.

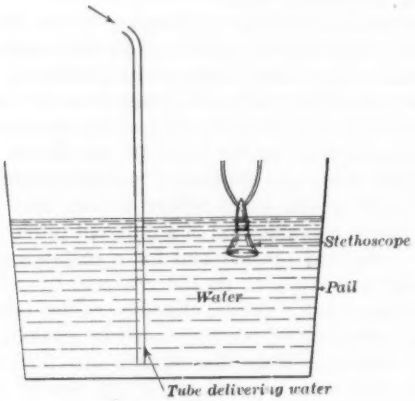

DIAGRAM II.

The comparison is limited to the aortic valve at which the conditions are seemingly simpler. In 56 of the 80 cases the valve was normal and no murmur was recorded. In 6 instances a systolic murmur was present; the postmortem findings were: 4 cases of organic stenosis, a fifth in which a much enlarged heart was associated with hypertension and arteriosclerosis, and in the sixth the valve was normal and the murmur not explained.

In the 18 cases remaining the aortic valve was disclosed to be definitely roughened from various sclerotic changes, in most of which calcification was present, and yet no systolic murmur at the base was recorded. It might be thought that in some of these cases the presence of a systolic murmur over the lower precordia might have caused one at the base to be overlooked. On this point it was found that of the 18 cases, without a systolic murmur at the base in spite of a roughened aortic valve, 5 did have a systolic murmur at the apex; in 3 of these organic changes of the mitral valve were evident and in the remaining 2 none.

In brief then, of 23 cases in which at autopsy the aortic valve found to be definitely roughened, in only 5 was a systolic murmur detected in life. In these latter sufficient cause other than roughness existed.

Comment. A review of the literature pertaining to the mechanism of the production of vascular murmurs appears to disclose that the most common and effective condition giving rise to a murmur is the *veine fluide*. This results from a true stenosis of the vessel or

an abrupt widening of its lumen. A sufficient degree of pressure and velocity of blood flow are necessary.

The second condition which favors the production of a murmur is that of a cul-de-sac against the current, as described by Bergeon. This factor is operative apparently when there is merely a sharp edge or lip opposed to the stream. It would seem that the structure of the mitral valve is such that a cul-de-sac against the stream is often present in addition to the conditions that produce a *veine fluide.*

There is a lack of agreement as to the importance of roughening of the inner aspect of the vessel. The difference of opinion is probably due to a difference in the experimental procedure used to determine the effect of roughness. Thus, as already mentioned, Theodor Weber's experiment, in which he stuck bits of cork to the inner aspect of a tube, would appear unsound. In his original report[6] Weber makes no statement as to the exact size of the small pieces of cork or of the amount introduced; in fact he has nothing to say as to what precautions he took to avoid introducing some degree of stenosis. The details of this observer's experiment are seldom referred to, but, if I am correct, his conclusions are often quoted and have exerted much influence in establishing the belief that roughness of the inner aspect of a vessel is an adequate cause for the production of a murmur.

Let us see what methods Chauveau used in getting the evidence on which he based the assertion that the asperities that roughen the internal surface of the circulatory tubes, without modifying the calibre of the latter, cannot be a cause of a murmur. He reports two experiments:

1. Ten to 15 cm. of the carotid artery in a horse were exposed surgically. When with a coarse string tightly drawn around the vessel he cut the lateral and median coats at four or five points rather near together. The coats of the artery torn by this constriction form, producing, to follow closely Chauveau's words,[4] rugosities on the inner aspect of the vessel. These rugosities can be made still more numerous and prominent by pinching the artery with forceps and thereby crushing irregularly the friable layers of the vessel wall. No murmur resulted from this experiment.

2. A metal tube of about the caliber of the artery in diastole was made rough in the interior by powdered gritstone blown in on collodion or varnish. The tube was then introduced into the course of the carotid artery. Result: no murmur.

Chauveau warned that great care must be used not to alter the caliber of the vessel in these experiments. He also pointed out that the clinical study of senile ossification of the arteries agrees with the above experiments in that roughness does not produce a murmur.

My experiments would tend to confirm those of this distinguished

Frenchman. I realize, however, the difficulty in satisfactorily testing the effect of roughness alone, but may say that this work has led to a conviction that if roughness is any factor in the production of vascular murmurs it is very slight and in no sense comparable with the cul-de-sac against the current or the conditions which produce a *veine fluide*. The clinico-pathologic findings reported above are in agreement with this view.

That the composition of the walls at the point at which the murmur is produced has an influence on the murmur would seem to be a logical conclusion from the experiments which I have described. An analogy is found in the alteration in the character of the aortic second sound which is observed when arteriosclerotic changes have occurred in the valve and adjacent aortic wall.

One of the best books on physical diagnosis states, "If the mitral curtains are fixed or made rigid by calcification, so that the vibration with the mitral direct current of blood does not take place, either the murmur may be wanting or its usual characteristic quality may be absent."[17] Another explanation for the absence of the murmur is suggested by certain observations of John Tyndall. The latter, in studying the sounds produced by the flame from gas burners, noted that a certain flame, that made a clear singing sound when surrounded by a long tube was silent when a shorter tube was substituted. He writes: "This large flame, in fact, is not able to accommodate itself to the vibrating period of the shorter tube. . . . But on lowering the flame it soon bursts into vigorous song, its note being the octave of that yielded by the longer tube."[18] Thus the physics of sound are such that certain relations must be present between the surrounding tube and the jet of gas or of fluid, which acts similarly, according to Tyndall, who exhaustively studied the subject, in order that a sound may be produced. It would seem probable, therefore, that the absence of a murmur in the type of mitral valve described by Flint is due to the phenomena observed by Tyndall, *i. e.*, a nonexistence of the relations between the jet and the surrounding tube that are necessary for production of a sound. The same laws must apply to the other cardiac orifices.

The experiment similar to that of Richard Geigel, with the stream of water flowing into the pail of water, is said to demonstrate that the sound is due to vibrations of the vessel walls. Eddies occur in the fluid, but unless they set the walls in vibration no sound is heard. The apt comparison by Theodor Weber of the *veine fluide*, eddy, and so on, to the bow and the vessel wall or valve to the string of a violin has already been mentioned. Apparently also the sound varies in accordance with what is set in vibration; an

[17] Flint's Physical Diagnosis, revised by H. C. Thatcher, Lea & Febiger, 1920, p. 283.

[18] Tyndall, John: "Sound," D. Appleton & Co., 1867, p. 225.

analogy to this are the sounds produced by a stream of water from a hose played upon a window pane and then upon the piazza floor.

In eddies and whirlpools the molecules of water or other fluid continue to move from the spot from which they started. This is a different phenomenon from sound which travels by waves transmitted from one molecule to another similar to the impact transmitted through a row of billiard balls.[18] A wave[19] is a disturbance which travels through any medium without permanently displacing the parts of that medium. Since fluids are practically incompressible, and certainly not so at any such pressure as exists in the human body, Bergeon's conception of alternate compression and reaction of the fluid at the point of murmur production does not seem satisfactory. The literature dealing with the question as to whether the sound originates in the fluid or in the vessel wall is extensive. It does not seem profitable for me to attempt further discussion of the point.

Vascular murmurs, being but one form of sounds, are subject to all the laws of the latter. Thus in their transmission to the surface of the chest considerable alteration may occur due to reflection and refraction as the sound waves from one medium to another of a different density. The sound may be increased by resonance, just as the hollow part of the violin acts with the sound produced by the vibrating string. Further discussion on these aspects of vascular murmurs is beyond the scope of this paper.

Conclusions. 1. A murmur is most readily produced where the conditions exist for the formation of a *veine fluide* or jet. Such conditions are:

(*a*) A stenosis or narrowing of the vessel.

(*b*) A sudden increase in the caliber of the tube.

2. A certain velocity of the stream is necessary.

3. Within certain limits the loudness or intensity of the murmur is proportional to the velocity of the stream.

4. The murmur is propagated both up stream and down, but better in the latter direction.

5. A second condition, easily giving rise to a murmur, is the cul-de-sac against the current. A mere sharp edge or lip is sufficient to cause a murmur.

6. The murmur produced by the cul-de-sac against the current is less intense than that associated with the *veine fluide*, and it is better transmitted up than down stream.

7. Roughness of the inner surface of a vessel appears not to be a cause of a murmur, or if this be not literally true then a murmur due to roughness of the vessel wall is very slight and in no sense comparable to those produced when a *veine fluide* or a cul-de-sac against the stream are present.

[19] Hall and Bergen: A Text-book of Physics, Henry Holt & Co., 1899, p. 443.

Earlier observers are not in agreement as to the influence of roughness of the vessel wall in the production of a murmur. In testing this experimentally great care is necessary to avoid the presence of stenosis also. This error appears to destroy the value if certain experiments, as a result of which some observers have concluded that roughness is a sufficient cause for the production of a murmur.

8. The conditions suitable for the formation of a *veine fluide*, a cul-de-sac against the stream and roughness of the vessel wall may be and often are present together in the human heart.

9. The quality of the murmur is influenced by the character of the vessel wall at the point of production.

10. In their transmission murmurs may be altered by the effect of resonance and of the reflection and refraction of sounds.

11. Murmurs are not mysterious phenomena incapable of explanation, but are one kind of sounds and are subject to the laws that the science of physics has shown pertain to sounds.

THE VALUE OF THE ROENTGEN RAY IN CARDIAC DIAGNOSIS.*

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According to an old adage, "Seeing is believing." The roentgen-ray has a greater appeal than the older methods of physical diagnosis in that it brings the living human heart within the range of that special sense upon which we place greatest dependence. Nevertheless, like many of the special methods of examination that have been introduced into clinical medicine in recent years, the roentgenologic examination of the heart has suffered in reputation from two causes; many not familiar with the type of evidence furnished by the method have expected too much of it; others, specializing in its use, have exaggerated its importance, making extravagant claims which have tended to bring it into disrepute. When it was first employed cases were reported in which sclerotic coronary arteries or an open foramen ovale could be visualized, and it was used by the advocates of special "cures" to demonstrate that certain systems of calisthenics or courses of baths had a definite and favorable effect upon the cardiac silhouette.[1] Looked upon

* Read by Dr. F. N. Wilson at a meeting of the New York Association of Cardiac Clinics, February 8, 1922.

as an ultrascientific method it is still considered by many a veritable *autopsia in vivo*. In its proper sphere, where it is used as an adjunct to our older clinical methods and not as a substitute for them, the roentgen-ray examination of the heart is an invaluable method; it has not failed and it cannot fail in the future to bring us more complete and accurate knowledge, but it is a method which we should be careful not to misuse.

A thorough and systematic study of the normal must always precede the investigation of the abnormal; the experience of the world war has recently emphasized the fact that many errors in diagnosis arise from an insufficient appreciation of the variability of the normal. In the case of the roentgen-ray our knowledge of the normal cardiac silhouette, in spite of the large amount of work that has been done, is still insufficiently comprehensive.

Appearance of the Heart on Fluoroscopic Examination. From the standpoint of the roentgenologist no other organ is so favorably situated as the heart. On ordinary dorsoventral fluoroscopic examination it stands out clearly as a deep shadow against the brightly illuminated lung fields to the right and left. This shadow is continuous above with that of the sternum, the vertebral column and the great vessels, and below with the shadow of the diaphragm and the structures that lie beneath it. The normal cardiac silhouette is bounded on the right and on the left by well-defined arcs corresponding to the lateral borders of the individual cardiac chambers and the great vessels. On the right there are two arcs: The lower is formed by the right auricle and the upper by the superior vena cava or by the more dense ascending aorta. On the left border three and sometimes four subdivisions can be made out; the uppermost arc is formed by the arch and descending aorta; the lowermost arc by the left ventricle; and the middle arc by the pulmonary artery; between the lowest and the middle arcs a fourth, formed by the left auricular appendage, may sometimes be seen. The cardiac apex is frequently lost in the shadow of the dome of the diaphragm which lies behind it; it is best seen when the cardiac end of the stomach contains a bubble of gas or during deep inspiration.

The position and shape of the normal heart varies greatly; in tall, slender individuals (asthenic habitus) with long, narrow chests the cardiac silhouette is also long and narrow and its longest diameter may be nearly vertical; in short, stout subjects (hypersthenic habitus) it may, on the other hand, be nearly horizontal. In persons of average build the longest diameter makes an angle of between 30 and 40 degrees with the horizontal.

The density of the shadow cast by the heart and the great vessels is not uniform. The shadow of the superior vena cava is very faint, so that the more dense aorta can be seen through it; the descending aorta is also visible in many instances through the structures

which lie in front of it. The shadow of the left auricular appendage and that of the apex are relatively faint. In some individuals with cardiac disease an indistinct shadow is seen running upward and to the right from the border of the left ventricle; it corresponds fairly well in position to the interventricular septum, which it was believed by Moritz to represent. Groedel[1] has observed it only in cases in which the left auricle was thought to be greatly enlarged and believes it is the shadow of the lower border of this chamber seen through the shadow of the ventricles.

By rotating the subject through an angle of 45 degrees, so that the rays pass through the chest obliquely or by lateral illumination, in which the rays pass through the chest from right to left, other views of the heart may be obtained. With these procedures the distance of the heart from the screen is considerably greater than with dorsoventral illumination and the depth of tissue which the rays must penetrate is much increased; the result is a greater exaggeration of the heart shadow and a marked reduction of contrast. The configuration of the cardiac silhouette in these positions and the identity of the chambers which form various parts of its outline vary according to the exact position of the subject with reference to the direction of the rays, and have been worked out much less fully than in the case of dorsoventral illumination.

With the subject in the right anterior oblique position, in which the rays enter the left back and emerge on the right side anteriorly, the posterior mediastinum appears as a clear band of uniform but variable width.[2] It is bounded on the posterior side by the vertebral column and anteriorly by the aorta in its upper third, the left auricle in its middle third and the right auricle in its lower third.[2] No definite arcs can, however, be made out. The anterior border of the cardiac silhouette is bounded below by the right or left ventricle according to the angle of view and above by the pulmonary artery. The aorta appears as a narrow band at the top of the shadow. The width of the clear posterior mediastinum increases with inspiration and decreases with expiration.

With the subject in the left lateral position we get some idea of the anteroposterior diameter of the heart. In the average normal subject it makes up about 0.7 of the total sternovertebral distance.[3] The posterior margin of the cardiac silhouette is formed by the left ventricle below, the left auricle in its middle portion and the aorta above; the anterior margin by the right ventricle and the pulmonary artery. The lack of contrast makes it very difficult, however, to distinguish details.

As Groedel[1] has pointed out, the lateral and oblique positions show that the longest diameter of the heart is not parallel to the anterior surface of the chest; it makes an acute angle with the vertical axis of the body; the heart is therefore foreshortened by

projection upon a plate or screen in contact with the ventral surface of the chest.

The Cardiac Pulsations. With dorsoventral illumination the pulsations of the heart can be seen plainly, but the amplitude of the movement varies greatly in different normal individuals. The movement of the right auricular border is usually so small as to be hardly measurable; the superior vena cava may be motionless or may show slight movement alternating with that of the auricle. The systolic pulsation of the aorta is easily seen though not of large amplitude; the pulsation of the pulmonary artery is less conspicuous. The greatest movement is shown by the border of the left ventricle; it differs in character from that of the right auricle and that of the great vessels, in that it is more deliberate and gives the impression of being more forceful. At the junction of the left auricle and the left ventricle there is a sort of walking-beam effect with a node of no motion which moves up and down with each cardiac cycle.

Our knowledge of these pulsation phenomena is as yet very imperfect and will remain so until some adequate method of recording them has been devised. Some progress in this direction has recently been made. Crane[4] has a method for taking what he calls "roentgenocardiograms." A lead sheet with a transverse slit about 2 cm. wide is placed between the patient and the plate in such a way that the slit overlaps the heart borders of which the movements are to be recorded. The plate is moved in front of the slit at a uniform speed. By this method tracings somewhat resembling pulse tracings may be made; those so far published have been rather poor from a technical standpoint, but this defect may perhaps be overcome. Flohil[5] and Eyster and Meek[6] have devised methods for taking instantaneous (exposure of 0.04 second) roentgenograms at chosen points in the cardiac cycle; an electrocardiogram is taken simultaneously, and this, through induction, records the time of the exposure with reference to the electrocardiographic deflections. Eyster and Meek have been able by using a special plate-changing device to take plates at the beginning and at the end of the same systole. From such plates they compute, using the tables worked out by Bardeen,[7] the systolic output of the heart. They find that "usually the maximum change is at or near the apex and decreases upward, but the reverse may be seen. The movement of any one point on the left border may give an entirely erroneous idea as to the extent of the contraction of the heart." They describe a typical cardiac contraction as follows: "When the auricles contract the right auricular border decreases slightly and there is a corresponding enlargement along the lower border of the left and right ventricles. The apex moves about 1 mm. to the left and the heart becomes slightly more

elongated from base to apex. . . . As the ventricles contract the right auricular border enlarges slightly and extends outward slightly more than immediately before the auricular systole. The bases of the ventricles descend a few millimeters and the whole heart becomes more globular in outline. The apex moves upward and to the right, the right ventricular border moves toward the base and the left ventricular border to the right." These observations are very interesting; it is to be hoped that they will be continued and that they will be extended to include instances of heart disease.

It is rather difficult to see, however, how it is possible to measure the movements of the right ventricular border and of the ventricular base accurately, for these borders are not clearly visible in the roentgenogram. It is also difficult to see the value of computing the systolic output by the method mentioned, for changes in auricular volume cannot be distinguished with certainty from changes in ventricular volume, since the position of the *A-V* junction cannot be accurately determined. It is quite within the range of possibility that in some instances the chief alterations in auricular and in ventricular volume are accomplished by changes in the position of the auriculoventricular septum. According to Van Zwaluwenburg,[2] hearts of the pendulous type often show more movement of the apex than hearts of the sessile type. He believes that in the former, which are in a way suspended from the great vessels, the *A-V* septum moves less and the apex consequently more.

Effects of Respiration and Change in Posture. The cardiac silhouette is altered in position and in form by the respiratory movements and by changes in the posture of the body. With forced inspiration the heart follows the diaphragm downward and the long diameter rotates in a clockwise direction.[5] The long diameter of the heart increases slightly while the transverse diameter decreases considerably.[1] There is probably also some torsion of the heart. Whether these changes in the position and shape of the heart are accompanied by changes in its volume has been much disputed; quiet breathing seems to cause comparatively little change in the size of the cardiac shadow. Cohn,[8] who has recently investigated this subject, found that in the majority of individuals both the long and the transverse diameters as well as the area of the cardaic silhouette were slightly greater in inspiration than in expiration. It has been shown that the Valsalva experiment causes a definite decrease in the size of the heart shadow while the Müller experiment causes a definite increase. Forced expiration and forced inspiration probably have similar though less marked effects. Forced expiration causes a greater shift in the position of the heart than forced inspiration when the subject is in the erect

position; the opposite is true when the subject is in the supine position.

The changes in the cardiac silhouette which accompany a change from the horizontal to the vertical posture are in part due to the change in the level of the diaphragm and the tendency of the heart to drop down of its own weight when the subject stands. There is, however, a definite decrease in the area of the heart shadow on assuming the vertical posture. The heart volume is said to be about 25 per cent less with the subject standing,[1] and the area of the cardiac outline to be about 13 per cent less.[8] The cause of these variations is not altogether clear; they have been attributed to traction on the cavæ and the pericardium in the standing position, to hydrostatic factors and to pressure of the dome of the diaphragm on that part of the heart which lies between it and the anterior chest wall in the lying position.

Of the changes in the cardiac silhouette which accompany other changes in posture nothing need be said; they are for the most part such as might be anticipated. It should be noted, however, that the pendulous heart is much more mobile than the more sessile organ, which is firmly held in the angle between the dome of the diaphragm and the anterior chest wall. On one occasion a tall, thin student consulted one of us because he found that when he lay on his right side the cardiac impulse was best felt to the right of the sternum; his heart was normal but of the pendulous type.

The Roentgen-Ray in the Diagnosis of Cardiac Enlargement. Upon few subjects that have received an equal amount of attention are there greater differences of opinion than upon the roentgenologic estimation of the size of the heart. In preroentgenologic days the clinician depended for this purpose upon the position and character of the apex-beat and upon the percussion outline of the deep cardiac dulness. How inadequate these methods are we all realize. Before the days of the orthodiagram there was, even among the masters of percussion, no general agreement as to the usual limits of the deep cardiac dulness in the normal subject. It is only within recent years that the percussion outline has been made to correspond with the orthogonal projection of the heart upon the anterior chest wall. But inaccurate though they be, inspection, palpation and percussion are very useful in judging the heart's size; they rarely lead to gross errors because we are familiar with their limitations. With the roentgen-ray with which they cannot compete in accuracy we are not altogether satisfied because we have, without reason, expected it to enable us to distinguish infallibly between a heart which is just beginning to enlarge as a result of disease and one which is normal. This is manifestly impossible; no sharp line can be drawn between health and disease; a zone of uncertainty is inevitable.

In the roentgenologic examination of the heart two methods

are available: orthodiagraphy and teleroentgenography. As a general method the former is certainly preferable; it is much less expensive and it allows us to mark the junction of the left auricular and the left auricular border and the junction of the right auricular border and that of the great vessels, and to follow the left ventricular border below the dome of the diaphragm. It gives us a view of the cardiac pulsations. Its chief disadvantages are that it requires more skill and is more subjective. When possible a combination of the two methods should be used.

Before the roentgen-ray could be used successfully in the diagnosis of cardiac enlargement it was necessary to establish normal standards. In establishing such standards it is desirable, in order to make the normal range as small as possible, to take into consideration all of the factors which are known to affect the size of the normal cardiac silhouette. It is known that the heart shadow varies in size with the body weight, the height, the posture, the heart-rate, the sex, the phase of respiration, the position of the heart and the amount of physical exertion to which the subject is accustomed. It must be remembered that the heart is an elastic organ; its size varies with the volume of its contents; the venous pressure, the intrathoracic pressure, the tension of the pericardium, the elasticity of the heart muscle probably play a part in determining the volume of the heart. It is true that the influence of many of these factors is probably so slight that no great error is made in neglecting them, but the normal standards at present in use take into consideration only the posture, the body weight and the phase of the cardiac cycle. The subjects are usually examined in the erect posture, the diastolic size of the heart shadow is determined and the subjects are classified according to weight.

As to the best method of measuring the size of the heart shadow there is no general agreement. The most popular method is to measure the area of the silhouette by means of the planimeter or to compute the approximate area by some formula such as that for the ellipse. One difficulty with this method arises from the continuity of the heart shadow with that of the great vessels above and that of the liver below; the upper and lower borders must be drawn in more or less arbitrarily before its area can be measured. The error is probably not great in dealing with the normal heart; it is certainly much greater in dealing with the abnormal heart, of which the shape varies greatly. Another difficulty, one which is common to all the roentgenologic methods of determining the presence of cardiac enlargement that have so far been proposed, arises from the width of the normal range. As Cohn[8] has recently pointed out, individual normal subjects may show silhouette areas larger by 30 per cent or more than the average area for normal subjects of the same weight. Similar deviations from the normal average have been found by all observers except

Smith;[9] they are therefore probably not to be avoided by any refinement or variation in technic.

The method in use in Ann Arbor was introduced by Van Zwaluwenburg. He found that by treating the cardiac silhouette as an ellipse and computing the area by multiplying the product of the long and short diameters by 0.7854, he obtained figures which showed an average deviation from the planimeter values of only 3 or 4 per cent; the greatest deviation amounted to 8 per cent.[2] He also found it convenient to express the area of the cardiac shadow of individual cases in percentages of the average area of normal subjects of the same weight. Since the area computed by this method is a constant fraction of the *product of the diameters* (*POD*), the latter may be utilized instead of the former as a measure of the heart's size. The average *POD* (in square centimeters) of normal subjects, expressed as a function of the weight, is approximately equal, according to Van Zwaluwenburg, to $3.72\sqrt[3]{\text{weight in pounds}}$.[2] This standard falls considerably below that of Bardeen.[7] A variation of 10 per cent in either direction is considered to be within normal limits. The subjects are examined in the erect posture and the cardiac silhouette is recorded by means of the orthodiagraph.

The smallest values observed have been in the neighborhood of 85 per cent, the largest in the neighborhood of 280 per cent. The great majority of abnormal hearts show values in excess of 130 per cent, but occasionally cases of mitral stenosis and of cardiosclerosis show values within 10 per cent of the standard figures. We frequently see, on the other hand, values as high as 140 per cent in cases in which no abnormality of the heart can be discovered by other methods and in which there are no clinical findings that would lead us to anticipate cardiac enlargement. It is possible that in such cases we are dealing with slight idiopathic cardiac enlargement, but we very much doubt that this is often the case. We believe that in most of these instances the heart is normal; the patients are usually asked to return in six months for a second examination.

Several other methods of diagnosing cardiac enlargement from the cardiac silhouette have been advocated. One that has recently received considerable attention is the determination of the ratio of the total transverse diameter of the heart (the total transverse diameter of the heart is the sum of the greatest perpendicular distance from the midline to the right border (*MR*) and the greatest perpendicular distance from the midline to the left border (*ML*)) to the internal diameter of the chest.[10] When this ratio exceeds a value of 0.50 the heart is considered to be abnormally large. In order to get a better idea of this very simple method we went over 60 orthodiagrams, selected at random, and compared this ratio with the *POD* expressed in the percentage of the standard. In 28 cases both methods indicated cardiac enlargement; the *POD*

varied between 116 per cent and 272 per cent, the ratio between 0.50 and 0.75. In 16 cases both methods indicated no cardiac enlargement; the *POD* varied between 85 per cent and 110 per cent while the ratio varied between 0.37 and 0.50. In 10 cases the *POD* indicated enlargement while the ratio did not; in one of these cases the *POD* reached a value of 150 per cent. In 6 cases the ratio indicated enlargement and the *POD* did not; in one of these cases a *POD* of 93 per cent was associated with a ratio of 0.63. We got the impression that the ratio varies greatly with the shape of the chest and the position of the heart. In individuals of asthenic build it may fall as low as 0.35, while in individuals of hypersthenic habitus it may exceed 0.50 even though the heart is normal. It tends to give high values in cases of arteriosclerosis of the aorta in which the heart is transversely placed. It would also seem that it must undergo considerable variations with the phases of respiration, for inspiration tends to increase the transverse diameter of the chest while it tends to decrease the transverse diameter of the heart. It has the additional disadvantage that great variations in the size of the heart produce only slight variations in the ratio.

In a third method of determining the presence of cardiac enlargement the total transverse diameter of the heart shadow is compared with the average value of this measurement in normal subjects of the same weight. The total transverse diameter has the advantage that it can be measured with a high degree of accuracy; the right and left margins of the heart stand out clearly against the lung fields so that there is no uncertainty in locating them as there is in locating the apex, which is necessary to the measurement of the long diameter, or the upper and lower borders of the cardiac silhouette, which are necessary to the measurement of the silhouette area. The chief objection to this method is that the transverse diameter varies with the angle of inclination of the long axis of the heart; when the heart is of the pendulous type the transverse diameter is very small; when the heart is horizontally placed the transverse diameter is relatively large. In Cohn's tables[8] the range of the transverse diameter for normal subjects of 74 kilos is 5 cm. In these tables the angle made by the long diameter with the horizontal is given for each subject; if we consider only those subjects (weighing 74 kilos) in which this angle varies between 40 and 45 degrees the range of the transverse diameter is reduced to 3 cm. If we had standards which took into consideration the inclination of the long axis of the heart the usefulness of the transverse diameter in determining the heart's size would be greatly increased.

In this connection it should be pointed out that the long diameter and the area are influenced in a similar fashion by the inclination of the long diameter of the heart to the axis of the body.[1] How

variable this may be we do not at present know, but the possibility that it may have an important influence upon the measurements mentioned must be borne in mind.

We must conclude that with the standards at present in use it is impossible for the roentgenologist to diagnose with certainty grades of cardiac enlargement that are not recognized or suspected by the clinician. This fact should be emphasized; failure to realize it is sure to do harm. There is need for a much more comprehensive study of the normal cardiac silhouette than has yet been attempted. In such a study all of the factors which are known to influence the size of the heart shadow should be included. Not only height and weight, but the body surface, the sitting height the heart rate, the age, the diameters of the chest, the angle of inclination of the long axis of the heart and the amount of physical exertion to which the subject is accustomed should be recorded so that the influence of each may be determined. The anterior-posterior diameter of the heart and the inclination of its long diameter with reference to the axis of the body should be measured. And finally the subjects should be selected with great care and should be reëxamined after from two to four years so that incipient cases of heart disease might be excluded; this could easily be done in any medical school where freshmen could be chosen as subjects and could be kept under observation until graduation. In this way the width of the normal range could probably be reduced considerably and the roentgen ray could be made much more serviceable in the diagnosis of cardiac enlargement than it is at present.

But even if all of the variables mentioned were included in the standard tables the normal range would probably still be relatively wide. The weight of the heart is probably much more constant than its volume, and certainly the weight of the heart can be determined with much greater accuracy than we shall ever be able to determine its volume by means of the roentgen ray. Nevertheless it is almost as difficult to diagnose cardiac hypertrophy after death as it is to diagnose cardiac enlargement during life. The figures of Müller[11] and of Lewis[12] show that the ratio ventricular weight body weight varies in controls within wide limits. Thus in Lewis's series of cancer controls, in which no cardiovascular abnormality could be discovered at autopsy, this ratio varies between 0.00200 and 0.00421, and has an average value of 0.00301. The individual variations are as great as those found by Cohn for the cardiac silhouette area. It is clear, therefore, that the normal range is not likely to be brought within narrow limits. Neither in clinical medicine nor in pathology is it possible to recognize the slighter grades of cardiac enlargement.

Variations in the Size of the Heart. In following the variations in the size of the heart in individual patients with cardiac disease

the roentgen-ray is vastly superior to any other method. For this purpose it is much better to superimpose successive teleroentgenograms or orthodiagrams than to compare measurements of these; errors due to changes in the position of the heart may thus be more easily avoided. The constancy of the heart's size in many cases of chronic heart disease is, as Grodel has pointed out, surprising. Such patients may go for long periods of time without measurable change in the cardiac shadow. A rapid increase in the size of the heart is usually of evil omen. We have recently seen, however, a case in which considerable variations in the size of the heart shadow took place without any appreciable change in the clinical condition. The patient was a young man with rheumatic aortic insufficiency and mitral stenosis; he had no cardiac symptoms whatever. The first orthodiagram showed a greatly enlarged cardiac shadow with a transverse diameter of 145 mm. The second orthodiagram, taken two months later, showed, when superimposed upon the first, a general increase in the size of the heart shadow; the transverse diameter was 172 mm. The third orthodiagram showed, when compared with the second, a slight decrease in the silhouette area; the transverse diameter remained about the same. The patient's clinical condition was unchanged.

The various therapeutic procedures, rest and digitalis, which bring about striking changes in the degree of heart failure, only occasionally give rise to a conspicuous decrease in the size of the heart. Patients are not usually examined by the roentgenologist, however, when the cardiac weakness is at its maximum, because of the technical difficulties involved. Most observers agree that a striking decrease in the size of the chronically enlarged heart is uncommon, and one observer states that when a conspicuous decrease takes place in such cases a pericardial effusion should be suspected.[1]

The case is quite difficult when the increase in size is not of long standing. Transient enlargement of the heart shadow has been noted frequently in various infectious diseases, including rheumatic fever, diphtheria, pneumonia and scarlet fever[1] and during attacks of paroxysmal tachycardia.[13] As to the exact factors involved in the infectious diseases we have no accurate knowledge. An increase in the size of the cardiac silhouette cannot, so it seems to us, be safely attributed to cardiac weakness unless it is accompanied by signs of venous engorgement or diminished blood flow. In paroxysmal tachycardia with increase in the size of the heart such signs have been observed.

The Recognition of Enlargement of Individual Cardiac Chambers. Most of the older text-books on physical diagnosis, and many of the newer ones, describe signs which are supposed to differentiate between hypertrophy and dilatation of the ventricles and between enlargement of the right and enlargement of the left ventricle.

Enlargement of the left ventricle is said to displace the cardiac impulse to the left and downward; enlargement of the right ventricle to displace the apex to the left. Left ventricular hypertrophy is said to cause a heaving apex-beat; right ventricular hypertrophy, to cause systolic retraction at the apex or in the epigastrium. Most of these signs, in so far as they have been tested by comparison with postmortem findings, have proved thoroughly unreliable. The electrocardiographic indications are likewise not to be depended upon.[14] It is, of course, possible to diagnose preponderant enlargement of the right or left ventricle correctly in many cases from a knowledge of the type of heart lesion present; we know that aortic insufficiency and chronic hypertension usually produce preponderant enlargement of the left ventricle and that mitral stenosis and pulmonary stenosis usually produce preponderant enlargement of the right ventricle. Such inferential diagnoses have little value. The roentgen-ray furnishes some real evidence of the size of the individual cardiac chambers, but here also caution is necessary in drawing conclusions.

The roentgen-ray signs of enlargement of individual cardiac chambers have been worked out by studying the shape of the cardiac silhouettes that have been shown to be characteristic of various valve lesions. It is difficult to check the roentgen-ray picture against the autopsy findings because of the changes in the heart which take place during the agonal period and after death through the occurrence of rigor mortis; nevertheless too little work along this line has been attempted. The relation of the component arcs of the normal cardiac shadow to the different cardiac chambers is no longer a subject of dispute; in the case of the abnormal heart, however, considerable difference of opinion exists. Much stress is often laid upon the character and time of the pulsations of a given border of the heart shadow in identifying the chamber which forms it; but since these pulsations have, heretofore, been studied by simple inspection only, and since the movements of a given arc are not solely due to the activities of the chamber of which it forms the margin, conclusions based upon such data must be looked upon with some skepticism.

There is also a tendency invariably to attribute increased saliency of a given margin of the cardiac silhouette to enlargement of the chamber which normally forms that margin, and to assume that increase in the size of a given chamber must invariably give the same picture. When we consider the great variability of the normal heart in size, shape and position it is hard to believe that this assumption is justified. It is to be expected that the picture of enlargement of a given chamber will vary greatly in individuals of different build. It must also be remembered that the heart is a mobile organ and its mobility differs in different individuals. When the enlargement of one of its cavities causes a shift in its

center of gravity it must readjust its position, and the new position like the old will depend upon a great many factors which vary from person to person. That auricular enlargement may be distinguished from ventricular enlargement in the majority of cases and that enlargement of the left auricle may be distinguished from enlargement of the right is hardly to be doubted. That the roentgenologist can say in every case of ventricular enlargement which of the two ventricles is chiefly affected remains to be proved. To show that certain signs held to indicate enlargement of the left ventricle only are present in aortic insufficiency and absent in pulmonary stenosis is not sufficient justification for considering these signs pathognomonic of left ventricular enlargement under all manner of conditions.

Hypertrophy and Dilatation; Cardiac Weakness. The roentgenologist can, in some measure, distinguish between hypertrophy and dilatation. Hypertrophy alone can, of course, cause comparatively little enlargement of the heart; the increase in the thickness of the heart wall which takes place when the heart hypertrophies rarely amounts to more than a few millimeters, and can hardly cause a recognizable increase in the diameters of the cardiac shadow. Recognizable cardiac enlargement means dilatation; if the enlargement has taken place within the space of a few hours it means dilatation alone. All chronically enlarged hearts are hypertrophied as well as dilated; the increase in size is due almost entirely to dilatation, but the shape may depend upon the amount of hypertrophy present. Viewed with the fluoroscope many enlarged hearts show well-defined arcs corresponding to the various cardiac chambers and a shape characteristic of the valve lesion present. Others appear shapeless; they are enlarged in all diameters and no distinct arcs are seen; the heart appears flaccid in that the shadow rests upon a broad base and is narrow above, so that it looks somewhat like a leather bottle filled with water; in such cases the pulsations are usually of small amplitude. The roentgenologist is prone to speak of hearts of the first type as hypertrophied and to describe hearts of the second type as dilated. Which of these forms the heart assumes when it becomes much enlarged may depend in part upon the chambers affected or it may depend upon the thickness of the ventricular walls.

The roentgenologist sometimes makes such diagnosis as "myocardial insufficiency" or "cardiac decompensation." In such cases he bases his opinion upon the presence of "dilatation" and upon the character of the cardiac pulsations. In describing the latter such terms as "feeble," "vigorous," "weak" or "strong" are used; we believe that such words should usually be avoided; they are apt to be considered descriptive of the condition of the heart muscle. The character of the pulsations seen on fluoroscopic examination is greatly influenced by the size of the heart, the

heart-rate and the position of the heart, and bears no close relation to the efficiency of the heart as a pump. Large hearts are usually bad hearts, but the terms *dilatation* and *cardiac weakness* are not synonymous. That there is a relation between the two conditions is not to be doubted; it is not, however, a close one. Very large hearts, more especially large shapeless hearts, are seen chiefly in patients who suffer or who have suffered from advanced cardiac failure; but a relatively large heart is compatible with fair cardiac function and a relatively small heart with poor function. The efficiency of the heart must be measured in terms of blood-flow; cardiac weakness must be diagnosed largely by the presence of signs and symptoms produced by a slowed circulation of the blood; for this purpose the examination of the heart itself is of quite secondary importance. In heart failure of the type associated with venous engorgement the right auricle is usually greatly dilated, so that there is a wide extension of the heart shadow to the right; this sign belongs in the same class with congestion of the liver and distention of the veins of the neck. Except in so far as this sign is of value in the diagnosis of cardiac weakness this diagnosis does not lie within the province of the roentgenologist.

The Diagnosis of Valve Lesions. Valve lesions can be diagnosed by roentgen-ray only in so far as they produce characteristic changes in the size and shape of the cardiac chambers affected, and thus alter the configuration of the cardiac silhouette and the saliency and pulsation of its component arcs. The roentgenologist is prone to regard these changes as a quantitative measure of the valve defect and to look upon valve lesions which are not associated with more or less characteristic alterations of the cardiac silhouette as comparatively unimportant. But the importance of a valve lesion does not depend solely upon the magnitude of the disturbance of cardiac mechanics which it produces; it depends even more upon the nature of the disease process to which it is due. In aortic insufficiency the clinician is, on the whole, less anxious to know the amount of blood which regurgitates than he is to know whether the lesion is a sign of arteriosclerosis, of syphilitic aortitis or of an old rheumatic carditis, or to know the nature and extent of the inflammatory and degenerative changes that have taken place in the ventricular muscle. In answering these questions the roentgen-ray, though less important than the history and physical examination, is often of service. The changes in the size and shape of the heart in chronic heart disease are not due solely to changes in the fluid pressures within its chambers, but in part to the associated myocardial changes. The roentgen-ray picture is often more significant in cases in which the cardiac silhouette is not characteristic of the valve lesion present than in cases in which it is.

In typical cases of mitral stenosis the cardiac outline is char-

acterized chiefly by an abnormal saliency of that arc which forms the margin of the left auricular appendage. This encroaches upon the left ventricular arc, which in the absence of left ventricular enlargement is shorter than in the normal. There is sometimes an abnormal extension of the shadow to the right of the midline; whether this is rightly attributed to enlargement of the right ventricle by Vaquet and Bordet[15] is questionable; it is by no means always present. The enlarged left auricle may also be seen by oblique illumination, in which it causes a constriction of the posterior mediastinum in its middle third (right anterior oblique illumination). When this picture is modified by rounding of the apex, by an increase in the length of the lower left arc, by an increase in the distance of the left border from the midline and by an increase in the anterior posterior diameter of the ventricular shadow the roentgenologist makes a diagnosis of mitral stenosis plus mitral insufficiency. Whether in such instances the ventricular enlargement is due entirely to the regurgitation of blood through the mitral orifice or whether the diagnosis of mitral insufficiency, mitral stenosis being present, has any particular value is, it seems to us, questionable. In some cases of mitral stenosis the pulmonary arc is prominent. Vaquet and Bordet[15] have described a case in which this was a conspicuous feature and in which there was a soft blowing diastolic murmur along the left border of the sternum which they took to be a Graham Steele murmur. Whether the Graham Steele murmur is a frequent phenomenon is still uncertain; we regard it as rare, believing that most of the basal diastolic murmurs which are so common in mitral stenosis are due to slight damage to the aortic valve. The origin of such murmurs, no changes in the pulse being present, is not of great practical interest.

In typical cases of aortic insufficiency the cardiac silhouette extends far to the left, whereas the width of the ventricular shadow (that is the diameter perpendicular to the long diameter) is not greatly increased. The apex is blunt and the arc of the left ventricle is lengthened and more sharply curved near the apex, so that the upper left margin of the ventricular shadow is sometimes described as "round-shouldered." According to Groedel[1] the apex is elevated, according to Vaquet and Bordet[15] it is depressed; its actual position probably depends upon the shape and position of the heart before the lesion developed and upon the presence or absence of changes in the aorta. The pulsations of the aorta are usually exaggerated; in rheumatic aortic insufficiency the aorta is of normal caliber while in syphilitic aortic insufficiency it is usually diffusely dilated. In the former mitral stenosis is often associated and a salient left auricle is added to the picture. Oblique examination shows an increase in the thickness of the ventricular shadow. The pulsations of the left border are deliberate and give the same impression of power that is gained from the heaving apex-beat.

Aortic stenosis is said to give a similar picture except that there is less enlargement and the aortic throbbing is absent. Chronic hypertension may give a picture closely resembling that of aortic insufficiency; the increased movement of the aorta is absent; the aorta is dense, lengthened and often diffusely dilated.

Open ductus arteriosus gives a cardiac silhouette characterized chiefly by abnormally salient and violently pulsating pulmonary arc. In pulmonary stenosis, which is very often associated with other congenital lesions, the apex according to Vaquet and Bordet[15] is often much elevated, so that the ventricular shadow resembles a "sabot" in appearance. We have not seen such a picture. Recently we have seen a patient with congenital heart disease and a loud systolic murmur with a pronounced thrill in the pulmonic area in whom the cardiac shadow was normal in every respect. An open ventricular septum is also said to give a characteristic cardiac shadow. In the cases which have been observed the silhouette was globular and extended far to the right and systolic pulsations of wide excursion were present at both right and left margins.[1 15]

Many roentgenologists believe that tricuspid insufficiency can be recognized by roentgen-ray examination. It is indicated when in addition to a greatly increased extension of the cardiac shadow to the right of the midline, produced by enlargement of the right auricle, the auricular arc and the vena cava show well-marked systolic pulsations. Whether this sign is more reliable than systolic distention of the liver and the positive venous pulse which were formerly much in favor is to be doubted. We cannot refrain from pointing out here to those who believe that tricuspid insufficiency causes recognizable expansile pulsation of the liver, that an increase of 30 cc, one-half the systolic output of the normal right ventricle, in the volume of a much congested liver with a volume of let us say 2000 cc, will cause an increase of less than 1 mm. in any one of its linear dimensions. Can a systolic distention of this magnitude be recognized through the abdominal wall and distinguished from mere nonexpansile movement? The case of the enlarged right auricle is similar; when one remembers that the movements of the margin of the normal right auricle are often barely visible he doubts the possibility of recognizing such systolic distention of a much enlarged auricle as could be produced by any amount of blood that is likely to regurgitate through the tricuspid orifice.

In *the diagnosis of diseases of the aorta*, arteriosclerosis, dilatation, syphilitic aortitis and aneurysm the roentgen-ray is exceedingly useful, but lack of space prevents us from considering this subject here.

Fibrinous pericarditis produces no roentgen-ray signs. Large *pericardial effusions* give large, roughly, triangular "water-bottle" like shadows which extend far to the right and rest upon a broad

base. The contour changes with changes in posture.[16] The silhouette borders are practically motionless. The cardiohepatic angle is maintained. It is sometimes difficult on a single examination to distinguish between a pericardial effusion and a very large heart; in such instances the clinical picture usually aids in reaching a decision. Small effusions are recognized with difficulty. The roentgen-ray has also proved useful in the *diagnosis of adherent pericardium* either through the visibility of extrapericardial adhesions or through the effect of the adhesions upon the mobility of the heart. The roentgen-ray diagnosis of adherent pericardium is, however, scarcely less difficult than the clinical diagnosis.

Conclusion. The roentgen-ray appears to us an indispensable instrument in the diagnosis of cardiac disease, but we must not allow the roentgenologist to make our diagnoses for us. We should ourselves be able to interpret his findings and to allot to them their proper place. We should be especially careful in the diagnosis of cardiac enlargement from the roentgen-ray picture alone, particularly in cases in which no cause for such enlargement can be found. Finally the exaggeration of the importance of the roentgen-ray examination of the heart, at the expense of other methods, which is to be seen in some of the recent French literature, is to be deplored. Special aspects of a subject are not to be neglected, but they must be subordinated to the subject as a whole.

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SUDDEN DEATH FOLLOWING THORACENTESIS.

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Clinicians of wide experience can usually recall in their own memories accidents and fatalities attending or following simple puncture of the thorax for either exploratory purposes, the drainage of fluid and more recently for the institution of an artificial pneumothorax in the treatment of certain cases of pulmonary tuberculosis. Notwithstanding the fact that these mishaps are comparatively uncommon and that the practice of thoracentesis is now considered a harmless and simple procedure, the well-known possibility of syncope, collapse and even death during or shortly following it should be sufficient grounds for regarding this procedure more seriously and inducing us to take any known precautions that may prevent the occurrence of untoward symptoms.

Physiologic Mechanisms. The physiologic mechanisms through which syncope, collapse and death are brought about have been the subjects of several signal investigations, and although it cannot be said that the mechanism is understood in every case, nevertheless certain facts have been demonstrated which rationally explains the mechanism in most cases. Russell[1] studied this subject in 1899, and he came to the conclusion that the syncope which sometimes attends or shortly follows simple thoracentesis is based upon direct injury to the vagus nerve fibers in the lung tissue with secondary reflex impulses conveyed to the heart. This explanation does not take into consideration any reflex which might arise and be propagated through the pleura itself, and is, in consequence, not in accord with the results of the splendid experimental investigations afterward performed by Capps[2] and his associates.

The Pleural Reflex. Capps's[3] interest in this subject was aroused by a fatal case of collapse which came under his observation in a patient with a pleural effusion. The collapse immediately followed the puncture of the pleural cavity after only a few cubic centimeters of fluid had been removed. The autopsy failed to reveal anatomic evidence for the cause of the unfortunate accident, although lesions such as laceration, hemorrhage and edema of the lung were sought as well as an investigation of the brain. It was to the careful experimental work of this investigator that clinical medicine owed the neurogenic conception of the mechanism of collapse in these cases. Capps proved the existence of a true pleural reflex, and any one interested in this subject cannot do better than review his original papers.[4 5 6 7]

By ingenious and convincing animal experimentation he showed

that the healthy pleura is tolerant to irritation, whereas the inflamed pleura may react to irritation, whether mechanical or chemical, by marked reflex circulatory disturbances. To use his own words he says, "The pleural reflex may act on the cardioinhibitory fibers of the heart through the vagus nerve-endings or on the vasomotor centers through the sympathetic nerves."

Capps's conclusions, based on his experiments, are as follows:

"1. Syncope during aspiration is the result of direct cardiac inhibition.

"2. Syncope during aspiration results from irritation of the pleural or pulmonary nerves either by the trocar or by congestion. It is most common toward the end of the operation when the instrument is most likely to scratch the pleura and when the lung is most congested.

"3. Syncope occurring within forty-eight hours after aspiration is probably due to the circulatory reflexes arising from congestion of the lungs.

"4. Syncope during irrigation of the pleural cavity is the result of a reflex arising from the chemical irritation of the pleura."

Pulmonary Lesions Produced by Thoracentesis (Injury and Congestion). Besides the foregoing fairly clear-cut type of collapse now believed to be due to the pleural reflex (often called pleural shock) there is another rather mixed group of cases which are seen but which have a varied pathogenesis. The cases referred to are, however, constant in one particular—in that they are practically always associated with demonstrable anatomic lesion of the lung parenchyma, either in the form of lacerations or puncture wounds caused by the trocar accidentally in the course of the thoracentesis or definite pulmonary congestion of an extreme grade.

Air Embolism. In 1912 Brauer[8] directed attention to the question of air embolism of the cerebral vessels. Stivelman,[9] in a recent paper, has been inclined not only to minimize the importance of this occurrence but to question its existence. More recently Spencer[10] has reviewed the literature on the subject of air embolism following thoracentesis and advances considerable evidence that the phenomenon is a physiologic-pathologic entity. Schlaepfer[11] quoted the case by Saugman of a young woman with pulmonary tuberculosis who was being treated by the artificial pneumothorax method. The trocar in this case was connected with a manometer and inserted 5.5 cm., when the manometer showed only small excursions, so a stylet was passed and on drawing this out a little blood followed. Immediately the patient felt giddy and the trocar was withdrawn. She turned pale and was laid on her back; she was unconscious and the head and eyes, with contracted pupils, turned to the left. Then the respiration became irregular and failed, the pupils dilated and she died. In this case it was found that the trocar had penetrated a vein in the lung and gas bubbles were

found in the bloodvessels at the base of the brain, including the sylvian artery. This instance, quoted by Schlaepfer, together with his review of the literature, afford clinical evidence of the existence and consequent results of air embolism involving especially the cerebral vessels.

Pulmonary Edema. In this mixed group of cases there occur those which present the well-recognized clinical picture of acute pulmonary edema. The phenomenon usually supervenes after the drainage of the pleural cavity, though it is known to occur after simple exploration. The exact mechanism of acute pulmonary edema has long been a moot question among pathologists, and in spite of the tremendous impetus of the late war to solve once and for all this perplexing problem it remains in dispute.

Schlomovitz[12] concludes his long paper, which is a critical review of the important work done on experimental pulmonary edema, with the statement that the mechanism of its causation must be sought beyond the immediately obvious causes, such as intravenous emboli, intravenous injection of drugs, injury to the chambers of the left heart, particularly the ventricle, electrical stimulation of the lung tissue directly, alterations in the content or the amount of blood, or any of the many other causes which have been advanced. It is conceivable that acute pulmonary edema may be the resultant of a group of causes.

Other Pulmonary Lesions. Pulmonary thrombosis, following lung puncture, with blood-clot embolism to the heart or brain, may also cause untoward symptoms. Pulmonary hemorrhage and congestion, with or without hemoptysis,[15] is at times the chief causative factor in the production of the disagreeable and dangerous sequelæ of thoracentesis. Albuminous expectoration is one of the well-recognized but less common results of pleural tapping.

In this mixed group, which has just been reviewed, it is more than likely that several of these factors combined account for the collapse in most instances.

Pneumothorax. Besides the mechanisms mentioned above, namely, the pleural reflex of Capps and this second group of cases with mixed pathogenesis, in which there are always demonstrable lung parenchyma lesions, there is one other condition of lesser importance that must be mentioned as a cause of untoward symptoms and even death. Numerous cases of spontaneous pneumothorax have occurred following exploratory thoracentesis, as pointed out years ago by Sears;[15] but since the institution of the treatment of pulmonary tuberculosis by the artificially induced pneumothorax method[16 17] the wealth of clinical experience offered by this procedure has shown that this sequel is not of serious import and is rarely the cause for untoward symptoms.[18] Doubtless many of the fatal cases reported in the older literature which were accredited to the accidental production of a pneumothorax follow-

ing exploratory thoracentesis, or the treatment of empyemas, or the withdrawal of pleural effusions, would in the light of our present ideas be better explained on the basis of the pleural reflex or pulmonary injury and congestion.

The following case stimulated my interest in this subject, and is presented rather completely both from the clinical and pathologic standpoint because it exemplifies an instance of a fatal accident following therapeutic thoracentesis.

CASE REPORT. *Clinical History.* The patient was a married woman, aged twenty-three years, who was admitted to the Urological Service of the San Francisco City and County Hospital on July 27, 1921, with the complaint of continuous sharp pain over the right side of the abdomen. The family history was essentially negative, she being the mother of three healthy children and with no history of miscarriages. The anamnesis disclosed the fact that she had had the usual children's diseases without known complications and also malaria at eight years of age and influenza at twenty. She had lost ten pounds during the three months previous to admission.

The present illness dated from November, 1920, with the onset of frequency of urination and incontinence of urine. The patient consulted a physician in April, 1921, who told her that she had "bladder trouble." During the last few months before admission she has been disturbed by some dyspnea, night-sweats and dull abdominal pain following her bowel movements.

The important findings made out in the physical examination at this time pertained to the chest, abdomen and the urine. There was slight bulging of the chest at the right base, and over this area expansion was poor, the percussion note was definitely impaired and both tactile fremitus and the breath sounds were absent. The right flank was bulging and there was an increased muscular resistance over the entire right abdominal wall. The pelvic examination was negative. A catheterized specimen of urine was reddish brown in color, contained many pus cells, with the polymorphonuclear type predominating; there were many bacteria present, but no tubercle bacilli could be demonstrated at this time in the centrifugalized specimen. The usual morphologic study of the blood showed: erythrocytes, 4,600,000; leukocytes, 17,000; a differential count with an increase of the mononuclear elements. The blood Wassermann was negative and the ordinary phthalein kidney function test showed a normal output for the two-hour period. Ureteral catheterization of the right kidney showed marked reduction of function on this side and a urine which contained much pus and some tubercle bacilli. A diagnosis of pyonephrosis of tuberculous origin was made and a surgical operation decided upon.

On August 5 a right nephrectomy was performed and a large

pyonephrotic kidney was removed. For several weeks following the operation the patient's condition was fairly satisfactory; however, the pulse, temperature and respiration remained elevated, which simulated the preoperative picture. The condition at the base of the right lung was thought to be due to a pleurisy with effusion, and this was concurred in by the fluoroscopic examination. Cystoscopic examination of the bladder showed a marked chronic, diffuse cystitis with secondary contraction.

On August 22, at 4 P.M., it was decided to perform an exploratory thoracentesis. The patient was elevated to the usual sitting position and the skin over the seventh interspace in the posterior maxillary line was anesthetized with a 1 per cent novocain solution. The exploratory trocar was attached to the usual 20 cc Luer syringe and the puncture was made at the above-mentioned point. The trocar was sharp and no undue resistance was observed by the operator. On an attempt to aspirate the pleural cavity nothing was recovered, and consequently the trocar was partially removed and then thrust forward in several directions. In the course of these explorations it was suddenly noted that an abrupt change had occurred in the patient. The first striking symptoms observed were the presence of cyanosis of the face and neck and a general stiffness of the body. This was followed rapidly by a loss of consciousness. Immediately after this condition was noted the aspirating trocar was withdrawn and measures were taken to relieve the apparent collapse. The head was lowered, adrenalin and atropin were administered subcutaneously and an ice-bag applied to the precordium. Within a few minutes after the onset of the symptoms the respirations became labored, tracheal rales were heard and considerable pinkish fluid was regurgitated by the mouth. Thereupon the breathing slowed and artificial respiration was begun, and this was followed by the administration of oxygen. The pulse had elevated and varied between 150 and 200. Unfortunately no blood-pressure determinations were made during the twelve-hour period of collapse before death. Within a half-hour after the mishap the reflexes were investigated and it was found that there was a definite jaw clonus present, the pupils were dilated and did not react to light, a bilateral ankle clonus was present and a positive Babinski was found on the right side, whereas it was doubtful on the left. During the next twelve hours the patient remained in this state of shock and at no time regained consciousness. The reflexes varied from time to time but the picture in general was constant. The patient died at 4 A.M. on the morning of August 23, just twelve hours after the thoracentesis and onset of the disastrous accident. A few moments before death a large amount of grumous, blood-stained material was regurgitated from the mouth. There were no involuntary movements of the bowels or bladder during the comatose state immediately preceding death. Although there

were various reflex disturbances, indicating cerebral irritation, there were no definite paralyses or convulsions.

AUTOPSY. The chief findings of the postmortem examination, five hours after death, were the following: General survey showed the body of a well-developed and fairly well-nourished woman of about her stated age. In the right posterior-axillary line, at the level of the sixth interspace, there was a small puncture wound. In the right lumbar region there was a long, recently healed, surgical scar, extending from the eleventh rib about 4 cm. from the spine downward and obliquely forward for about 16 cm. to the crest of the ilium, reaching a point 5 cm. posterior to the anterior-superior spine of the ilium. The lower angle of the wound presented a draining sinus and at the upper angle there was a small fluctuant area.

Abdomen. The abdomen was opened by the usual midline incision. The peritoneum appeared normal except in the region of the hepatic flexure, where there were fibrous adhesions binding this flexure and the posterior-inferior surface of the liver high up to the posterior abdominal wall and the diaphragm. There were numerous fibrous adhesions about the spleen. The mesenteries of the ascending and descending colons were unusually long. The stomach was tremendously dilated and was filled with a black liquid.

Pleural Cavities. The diaphragm was in the normal position. The left pleural cavity was practically obliterated by dense fibrous adhesions, whereas the right cavity also showed the same general condition, except that the adhesions were less numerous and dense. There was no free fluid in either pleural cavity.

Pericardial Cavity. The pericardium was normal and there was no fluid in the pericardial sac.

Heart. The heart appeared about normal in size and weighed 220 gm. The epicardium was smooth and glistening and the myocardium was of good color and consistency and showed no scars or areas of necrosis. The endocardium and the valves were normal throughout. The valve measurements were normal and the coronary arteries were negative.

Aorta. The aorta was normal in position. The intima was smooth and delicate.

Lungs. The surfaces of both lungs were extensively roughened by the thick, dense, pleural adhesions mentioned above. The lungs were moderately voluminous, hypercrepitant, and on section appeared to be markedly edematous; scattered throughout there were noted numerous moderate-sized, irregular, hyperemic areas. From the cut surfaces of both lungs considerable frothy, pinkish fluid exuded, which, however, did not appear blood-stained. In some areas there was also a certain small amount of pus which could be pressed from the bisected bronchioles. In the posterior portion of the left lower lobe there was seen a depressed, dark-colored, irregu-

lar area which measured 2 x 3 cm. in diameter. On section through this area there appeared a poorly defined, dark, bluish-red area slightly firmer than the surrounding tissue and extending for about 2 cm. into the cut surface of the lung. In the upper lobe near the apex on the left there was a firm, grayish-yellow, opaque, raised area about 1 cm. in diameter which was surrounded by a narrow, pale, translucent zone. Considerable interest centered around the right middle lobe, which on section presented several moderate-sized, dark-bluish, slightly raised areas. In the center of one of these dark areas there was a definite puncture wound. The entire lung parenchyma in this region disclosed the fact that the midlobe was the seat of extensive hemorrhage. This hemorrhage extended down to the region of one of the large branches of the pulmonary vein, but actual rupture of the wall of this vein could not be demonstrated. No clots were found in the bronchioles supplying this portion of the midlobe. The larger bronchial branches in both lungs contained a considerable amount of frothy fluid.

Liver. The liver was slightly enlarged and over the cut surface there were scattered irregularly a few small, round, yellowish-brown, opaque areas which were less than 1 mm. in diameter. The gall-bladder and ducts appeared normal.

Spleen. The spleen was large and the capsule was attached to the inferior, left, diaphragmatic surface by diffuse adhesions. On section the spleen showed nothing remarkable.

Intestines and Pancreas. These structures were normal.

Mesentery. The mesentery was normal except for the adhesions mentioned above.

Lymph Nodes. The posterior mediastinal lymph nodes appeared somewhat enlarged. There was no definite involvement of either the mediastinal or the retroperitoneal nodes.

Kidneys. The right kidney was absent (nephrectomy six weeks before death). The left kidney was slightly enlarged, weighed 200 gm., and the capsule stripped readily, leaving a brownish-red surface. The cut surface of the bisected kidney showed normal markings, however; the cortex was somewhat increased in thickness, measuring 7 to 8 mm. in diameter. The glomeruli were readily visible as white points. The medulla was also moderately increased in thickness and was sharply separated from the cortex. The renal pelvis, ureter and vessels appeared normal. In the right lumbar region, at the site of the nephrectomy, the tissues were diffusely thickened and scarred, involving the psoas muscle as well as the fascia and the adjacent fibro-fatty tissues. The region lying immediately below the skin under the operative scar presented a surface covered with necrotic tissue, in the midst of which were seen numerous small, opaque granules, while section through the upper portion of this tissue mass disclosed the right adrenal

buried within the dense tissue. The gland, however, showed no evidence of tuberculous involvement. The left adrenal was normal.

Bladder. The urinary bladder was small. The mucosa showed an extensive, irregular, rather superficial, ulcerative process scattered over its surface, together with numerous small, semitranslucent nodules. The ureteral orifices were situated at some distance from the urethra. The one on the left was readily found and was more or less surrounded by definite tubercles, whereas the right orifice presented a funnel-shaped depression while the tissue surrounding it was extensively involved in the tuberculous ulcerative process. The distal bladder portion of the left ureter appeared normal; on the other hand the right ureter showed a marked thickening of the wall throughout, with small, scattered ulcerations over the mucosa.

Brain. Permission was not obtained to remove the brain.

Complete Anatomic Diagnosis. Right nephrectomy; marked tuberculous ulcerative cystitis; marked tuberculous involvement of the right ureter; extensive tuberculous inflammatory reaction in the tissues of the right lumbar region with burial of the left adrenal in the fibrous tissue; fibrous adhesions about the hepatic flexure and the posterior-inferior surface of the right lobe of the liver; small focus of pulmonary gelatinous and caseous pneumonia in the left upper lobe; extensive pulmonary edema; disseminated hyperemic foci in both lungs; slight purulent bronchitis; puncture wound of the midlobe of the right lung with moderate hemorrhage into the pulmonary tissue; recent hemorrhagic infarct in the lower lobe of the left lung; diffuse pleural adhesions bilateral; acute gray splenic tumor; perisplenic fibrous adhesions; parenchymatous degeneration of the viscera; moderate endothelial hyperplasia in the retroperitoneal and mediastinal lymph nodes; marked dilatation of the stomach with "coffee-ground" contents; moderate compensatory hypertrophy of the left kidney.

Conclusion. In the foregoing case, it is obvious from the autopsy findings, outlined above, that the collapse during exploratory thoracentesis and the subsequent death of the patient within twelve hours of the puncture were not produced primarily by the pleural reflex, or, on the other hand, by the production of an accidental, rapidly formed, spontaneous pneumothorax. The puncture wound in the middle lobe of the right lung, which was surrounded by hemorrhage and congestion, in association with the presence of extensive pulmonary edema, justify the supposition that this accident was caused by the combined physiologic-pathologic mechanism discussed as our second group, namely, injury and congestion of the lung parenchyma plus acute pulmonary edema with secondary circulatory reflexes, appear to have been responsible for the fatal outcome. Nothing was observed either in the clinical picture or the autopsy findings to suggest that air embolism was a factor.

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DIFFUSE GLOMERULO-NEPHRITIS.

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With the increasing knowledge of kidney disease our viewpoint has gradually undergone transformation. We have learned to separate the various forms of tubular nephritis or nephrosis as definite entities. We have learned to separate the purely arterio-sclerotic kidney. In the realm of glomerulo-nephritis or nephritis proper, we have learned to separate the focal and embolic forms from the diffuse forms. In the diffuse forms the conceptions are still much confused, and in spite of the immense amount of work on the pathology of the kidney and on the blood chemistry there is still little proper understanding of the processes involved. This paper is written with the object of giving a clear view of this disease and especially to give due prominence to Volhard's theory of the pathogenesis of diffuse nephritis, which has not been sufficiently appreciated.

To understand the disease processes involved one must continually realize that diffuse glomerulo-nephritis is in point of time an extremely variable process. It always has its origin in an acute form, often in early childhood. When it passes into a chronic form it may only last a few months or may stretch over years, and may even find its terminal stage more than twenty years later. The pathologist who studies such kidneys sees the changes at the time of death only, and these are often complicated by the addition of recent and acute changes to the old and chronic ones, as well as by the secondary changes in the arteries and arterioles.

The pathology of diffuse glomerulo-nephritis has been definitely placed on a firm footing by the work of Nauwerck[1] and of Langhans[2] among the older writers, and the recent investigators especially by Loehlein,[3] Fahr,[4] Herxheimer,[5] Jungman[6] and others.

The following description of the pathologic histology of the kidney is from the work of the above-named authors.

Acute Diffuse Glomerulo-nephritis. The earliest pictures are characterized by a more or less equal involvement of all the glomeruli. The glomeruli are enlarged, entirely filling the capsular space and often protruding into the neck of the tubule. The individual capillaries are enlarged, swollen and there is an increased number of nuclei partly belonging to endothelial cells but mostly to a greatly increased number of leukocytes which can be demonstrated, as Graff[7] has shown, by the oxydase method. The loops of the capillaries are especially characterized by their bloodlessness while the intertubular capillaries are filled with blood. The

walls of the glomerular capillaries are thickened, and the lumen is empty of blood but contains a granular protoplasm in which the proliferated endothelial cells and the leukocytes are embedded. Here and there the glomeruli are sprinkled with fat droplets.

The capsular epithelium shows at this stage cloudy swelling, fatty degeneration with beginning proliferation of cells. In the capsular space here and there where the glomerulus does not quite fill it some red cells and coagulated albumin may be seen.

The convoluted tubules show cloudy and fatty degeneration and in some areas desquamation of cells. These are secondary to the changes in the glomeruli especially to the bloodlessness. It is the bloodlessness of the glomeruli which dominates the pathologic picture of acute diffuse glomerulo-nephritis, and it is the intensity and duration of the bloodlessness which dominates the further progress of the disease.

There are four possibilities in the further developments of this disease.

1. The capillaries of the glomeruli are again filled with blood, the swelling lessens and the glomeruli gradually return to normal. Of course, kidneys showing such a return to normal of the glomeruli are rarely seen post mortem and are only obtained when death is due to some complication occurring just at this time. Volhard and Fahr[8] describe such a case. Herxheimer's[9] cases X and XI are such cases.

2. The bloodlessness persists in its intensity and the changes in the glomeruli are rapidly progressive. The capillaries of the glomeruli are now shrunken and partly hyalinized and contain an increased amount of cellular elements. The proliferation of the capsular epithelium increases and forms concentric and semilunar masses of cell layers, which also become partly hyalinized and contain fat droplets. They fill the capsular space and are often larger than the glomerulus.

The tubules are dilated, atrophied, the cells are flattened, degenerated and the lumen is filled with casts. The interstitial tissue is here and there infiltrated with round cells and young connective tissue. The vessels show a proliferation of the intima.

This is the severest form. It corresponds to the extracapillary form of Volhard and Fahr and has been termed subacute nephritis by Volhard.

3. In this form the bloodlessness is not quite complete and here and there in the first divisions of the vasa afferentia blood may be seen. The glomeruli show a variety of pictures. The capillaries are broad, their walls thickened and partly hyalinized, some glomeruli are entirely hyalinized. The capsular epithelium is not proliferated but is surrounded by concentric layers of connective tissue. The tubules are dilated, regeneration of tubular cells is found here and there, but fatty and lipoid degeneration predominates throughout.

The interstitial tissue is markedly increased and also contains fats and lipoids. The vessels, especially the small ones, show definite proliferation of the intima. This form, which may last for a long time, has been termed by Volhard the subchronic form and corresponds to the intracapillary form of Volhard and Fahr.

4. This forms the secondary contracted kidney. The markedly increased connective tissue dominates the picture. It is irregularly distributed and in places infiltrated with round cells. Embedded in the connective tissue are masses of hyalinized glomeruli and atrophied tubules. Scattered among these are areas containing enlarged glomeruli of normal appearance and of normal blood content. The tubules belonging to these glomeruli are dilated, their epithelium is low, and fatty degeneration may be seen. Some of the glomeruli may be seen to be partly hyalinized and surrounded by concentric formations of connective tissue. The vessels, the large as well as the small ones, show marked arteriosclerosis with proliferation of the intima and splitting of the internal elastic membrane, and fatty degeneration, while some vessels are completely occluded. This is the chronic form or endarteritic form of Volhard.

In viewing the histological pictures one important fact stands out clearly, namely, the bloodlessness of the glomeruli and the reaction to this bloodlessness. This is the prime factor and its importance is insisted upon by Loehlein and more so by Volhard and Fahr. The changes in the tubules are secondary to it. In the acute diffuse glomerulo-nephritis it is the bloodlessness of the glomeruli which causes the infiltration of leukocytes and proliferation of the endothelial cells. It is the intensity of the bloodlessness which determines the severity of the acute form, and it is the duration of the bloodlessness which determines whether the changes in the glomeruli will retrogress and their capillaries again become permeable to the entrance of blood or whether the glomerular changes will become progressive, resulting in the subacute and subchronic forms. If the intensity or completeness of the bloodlessness of the glomeruli is marked and the duration sufficiently prolonged, the capillaries of the swollen glomeruli gradually begin to shrink, and the capsular space which is now functionless becomes filled with the proliferated capsular epithelium and at times with a leukocytic and hemorrhagic exudate which also becomes hyalinized. The permanent marked diminution of the blood supply results also in the changes in the tubules previously mentioned. These changes and their variations, resulting from the bloodlessness of the glomeruli which form the characteristics of the subacute form, determine the duration of the disease. As these changes, once established, are not retrogressive a fatal outcome is necessarily the result in the subacute form.

The subchronic form results when the duration of the blood-

lessness is sufficiently prolonged, but is much lessened in intensity and completeness. The glomeruli are really not bloodless but blood-poor, and although some capillaries contain blood, most of them do not, and have undergone permanent changes with shrinkage, and resulting increase in the interstitial tissue. The duration of this form, whether months or years, depends upon how much the capillaries again become permeable to the entrance of blood; and also whether the pressure necessary to force the blood through the capillaries is available.

All the variations in the histological pictures, as well as in the clinical forms, depend, therefore, upon these factors. (1) The duration and intensity of the bloodlessness. (2) The extent of the proliferative and infiltrative reaction as a consequence of this bloodlessness. (3) The extent to which, in spite of these reactions, the capillaries of the glomeruli can again become filled with blood.

The very chronic form, in which the glomeruli remain normal for many years after the subsidence of the acute stage, and which however, eventually results in the histological pictures described above, is more complex and we shall return to this form later.

The essential element and the starting point is the bloodlessness of the glomeruli. All the recent investigators in this field insist on this point. It has been assumed that this bloodlessness is secondary to the changes in the glomeruli. Volhard,[10] who has brought to the study of the nephritides a greater understanding and insight than any other worker in this field, has proposed a new explanation for this bloodlessness of the glomeruli, which gives a new viewpoint to the whole pathogenesis of the disease. Volhard comes to the conclusion that the starting point of all forms of diffuse glomerulo-nephritis and the cause of the bloodlessness of the glomeruli is a spastic contraction of the arteries above the afferent artery to the glomerulus; and that everything we have said above as resulting from the bloodlessness of the glomeruli is in the last instance the result of the intensity and duration of the spastic contraction. The arterial narrowing is at first functional and not the result of organic changes in the vessel wall, but with the duration of this spastic contraction organic changes result in the vessel below the choking, as well as in the glomeruli. The changes in the vessel wall below the point of choking have the character of a proliferating endarteritis with a consequent permanent narrowing of the lumen. As long as the choking of the blood stream is due to a functional spastic contraction the vessels may again become permeable when the choking is released. Once the organic changes have developed it depends upon their extent whether the vessels become permeable and to what degree. In the acute diffuse form the blood-vessels may always become permeable, but with the organic changes in the blood-vessels definitely developed it depends upon the intensity and extent of these organic

changes, whether the disease passes into the rapidly fatal subacute form, or into the slowly progressive and fatal subchronic form.

This theory of acute ischemia of the glomeruli, at first functional and due in the progressive cases to organic changes in the vessels and glomeruli, is of very great importance. Volhard observes, in the support of this theory, that he has found in kidney sections obtained at operation for decapsulation of the kidney, that the proliferative changes in the glomeruli were minimal, although the glomerular capillaries were bloodless. In support of the functional origin of the ischemia, he observes that he has been able in some cases in the early acute stage to relax the choking of the vessels by the single administration of a large quantity of water. This release would not have been obtained if the choking were of organic origin. He also observes, in support of this theory, that the acute form may heal without leaving any changes in the vessels or glomeruli.

Huelse,[11] in discussing Volhard's theory, remarks that while there are some objections to the theory that have not been overcome, no critic of this theory has been able to supply anything more plausible.

With the assumption of an angiospastic ischemia of the glomeruli as the beginning of diffuse nephritis, we enter the field of functional processes and changes. Our problems here are as follows:

1. What is the normal control of the flow of blood to the glomeruli, and what effect have the normal variations of this control on the function of the kidney?

2. How is the excessively increased control which results in an angiospastic ischemia of the glomeruli brought about?

3. What is the effect of this ischemia on the function of the kidney, and how is this effect compensated?

4. How can the clinical phenomena be explained on the basis of this ischemia?

The function of the kidney is to eliminate the nitrogenous waste products of body metabolism, to eliminate promptly any excess of water in the body, and to help maintain the constancy of the blood volume and blood composition. An excess of fluid intake is at once eliminated by the kidney in a urine of low specific gravity. Diminution of the fluid intake causes the kidney to produce a highly concentrated urine so as to save the water and certain salts for the body economy. It is not necessary here to enter into the age-old controversy between secretion on the one hand and filtration and reabsorption on the other. A mediating view has been put forward by Metzner[12], who assumes filtration by the glomeruli and reabsorption as well as secretion by the tubules. Recently Cushny[13] has most thoroughly presented the case for the filtration and reabsorption theory. Glomerular filtration is

practically assumed by all leading physiologists, and recently Richards[14] has added some new evidence, especially as to the role that the blood-pressure plays in the urine formation. Filtration and reabsorption can be said to be definitely proven, and we must discuss our first problem on this basis.

We know that the kidney can eliminate an added intake of more than 12 liters in twenty-four hours. We know that in diabetes insipidus 10 to 12 liters of urine can be eliminated daily. We know that to produce such quantities of urine enormous quantities of blood must pass through the glomeruli. What is the control that prevents, normally, in everyday life, such quantities of blood plasma from being filtered through the glomeruli? The answer is, in the extensive vasomotor control of the small vessels of the kidney and in the normal shutting off of a great number of glomeruli from active function. Richards, in the Harvey lecture mentioned above, quotes Hermann to the effect that one part of the excreting surface of the kidney may rest or be active, while another part is held in reserve. Richards and his co-workers have been able to observe the active glomeruli in the lateral border of the ventral surface of a frog's kidney by focussing the light of an arc lamp on the kidney. They have observed that the number of glomeruli that could be seen in a field varied and could be made to vary with the introduction into the blood of various substances. This led them to conclude that all the glomeruli of the kidney of the frog do not receive blood simultaneously. Injection of saline increases the number of the glomeruli; adrenalin lessens the number seen. When we realize that the effect of adrenalin is on the sympathetic nerve endings of the small vessels, and consider the experimental evidence of diminution of urine production by the stimulation of the renal nerves, and the increased flow of urine from cutting these nerves, it is evident that we have in the vasomotor mechanism of the kidney an extremely sensitive control of the blood supply to the glomeruli. The sensitiveness of this control can be judged from the easy reflex response to various distant stimuli, such as catheterization, cerebral injury, chilling of the body surface and others. It is this extremely sensitive control which regulates the amount of blood which passes through the glomeruli and in consequence the amount of urine formed. So sensitive is this mechanism that it responds with a diluted urine to a fluid intake which dilutes the blood so slightly that it cannot be detected by ordinary methods (Cushny).

What is the effect of the variations of this vasomotor mechanism on the function of normal kidney to eliminate water and nitrogenous waste products, and to keep the blood volume and composition constant?

We understand the function of the glomeruli to be that of filtration of a deproteinized plasma from the blood, which is then

concentrated in the tubules by the reabsorption of the water and those salts which the body needs for its economy, in a solution comparable to that of Locke's fluid, while the rest appears as urine. The quantity reabsorbed and therefore the concentration of the urine depends upon the length of time the glomerular filtrate remains in the tubules, and this again upon the flood coming from the glomeruli. It is obvious that with the sensitive mechanism which opens and shuts the vascular gates to the glomeruli in response to varying amounts of blood dilution, we have the explanation of the ability on the part of the kidney to produce a highly concentrated urine on water starvation, or to produce an extremely diluted one after a debauch on immense quantities of liquids and liquors.

When the vasomotor control is so stimulated as to shut off all the blood to the glomeruli, kidney function ceases and anuria results, and in this we have the explanation of the various reflex anurias. These are usually temporary. It is the sufficiently long duration of this angiospastic shutting off of the blood to the glomeruli, which forms, according to Volhard, the ischemia of the glomeruli, which is the beginning of diffuse glomerulo-nephritis. What produces this excessive vasomotor shutting off of the vessels to the glomeruli? This question, of course, coincides with that of the etiology of diffuse glomerulo-nephritis.

The etiology is unknown. Despite all possible speculation concerning the cause of glomerulo-nephritis, we are still no nearer the solution. That it is of an entirely different variety than the causes of the focal glomerulo-nephritides is at once obvious. In the latter we have local inflammatory reactions at the seat of the invading organism, a true defensive reaction involving only a portion of the glomerulus and only that portion where the invading organism happened to lodge. The rest of the glomerulus is free to carry on its function and there is usually enough of it left to do it. In acute diffuse glomerulo-nephritis there is no chance involvement of a glomerulus, but all the glomeruli of the kidney and with the exception of the very rare cases of unilateral glomerulo-nephritis, all the glomeruli of both kidneys are equally involved and to a more or less equal degree at the beginning. Whatever the cause, it must naturally have a central point of attack, and with the assumption of an angiospastic ischemia as a starting point, it must be something that will attack either all the vessels supplying the glomeruli or the vasomotor control of these vessels. This is perhaps comparable to the phenomena of anaphylaxis such as the contraction of the bronchial musculature in the guinea-pig, or the contraction of the pulmonary arterioles in the rabbit. For both of these possibilities, that is, for a reflex angiospastic contraction, and for the possibility of its being an anaphylactic phenomenon, there are suggestions in the literature.

The vasomotor supply of the kidney has its origin, according to Gaskell,[15] in the renal ganglion, and the connector fibres are to be found in the thoracico-lumbar outflow of the sympathetic nervous system, in the roots of the spinal nerves from the fourth dorsal to the fourth lumbar, while the skin and the blood-vessels are supplied with nerve fibers from the same thoracico-lumbar outflow. Exposure to cold causes afferent impulses to travel by way of the somatic nerves with reflex vasoconstriction resulting in blanching of the skin, increase in blood-pressure due to constriction of the splanchnic vessels, and diminution of the urine due to constriction of the renal vessels.

Exposure to cold is often given in the literature as a causative factor in nephritis. The tendency has been to discredit this factor and ascribe the nephritis to an accompanying affection. Krehl[16] says that "it is the experience of our best physicians that inflammations of the kidney are produced by the influence of intensive cold on the skin," and speaks of a "mysterious connection between the skin and the kidney." That a history of recent exposure to cold is often obtained in cases of acute nephritis is everyday knowledge. Classical cases have been reported. Horn[17] reports the case of a stoker on a steamboat who fell into the Rhine and on the next day had pains in the kidney region followed by acute nephritis with edema and hematuria. Experimentally, Siegel[18] produced a parenchymatous nephritis in dogs by the application of ice to the exposed kidney and by chilling of the hind legs and lumbar region. Others who repeated his experiments were not so successful.

In the etiology of war nephritis especially, exposure to cold and wet played a great role. Ameuille[19] quotes Chiari and Bruns who "maintain in no uncertain terms that it is almost always the chief cause." Bruns says that "in 70 per cent of the patients there is a clear history of a chill or exposure to dampness and cold." Ameuille himself does not agree with this. Fahr[20] quotes a number of writers who report cases of nephritis with chilling of the body as the causative factor.

For the second suggestion, that the angiospastic glomerular ischemia may be an allergic or anaphylactic phenomenon, there are several points in its favor. We know that nephritis often begins after an infection and especially a streptococcus infection, such as tonsillitis. We know that usually a week or more intervenes between the onset of the tonsillitis and the beginning of the nephritis. We know that the nephritis following scarlet fever always occurs nineteen to twenty-one days after the onset of the scarlet fever. All of these facts suggest resemblance to allergic reactions. Volhard also remarks that he has observed a true hydropic nephritis following vaccination for typhoid fever. Longcope[21] produced changes in the glomeruli and tubules by the injection of foreign

protein. Wells,[22] in reviewing anaphylaxis in Physiological Reviews, observes that in anaphylaxis, "presumably, stimulation of unstriped muscle tissue is universal," and "the symptoms observed depend upon the degree of development of these muscles, or their strategic location, in different organs of different species." Disse[23] says that "in the interlobular arteries of the kidney, the walls are very thick. The medium has very little elastic tissue, but has a large amount of muscle fibers." Perhaps the increased development of the muscular coat of these vessels in the kidney, and which may be still more developed in certain individuals as a result of hereditary tendencies, may play a role in the anaphylactic phenomena of the human being.

All these may be very suggestive and still we must repeat that we do not know as yet the cause of the angiospastic renal ischemia.

What is the effect of the angiospastic glomerular ischemia on the function of the kidney and how is this effect compensated?

In discussing the bloodlessness of the glomeruli, we have spoken of its intensity and duration. We mean by its intensity, the degree or completeness of vascular contraction. If this is extreme, and if it is not overcome, as we shall see later that it can be, no blood enters the glomeruli and anuria is the result. Anuria often ushers in an acute diffuse nephritis, and those cases which succumb in the early stages of acute nephritis show practically the absence of red cells in the glomeruli before any exudative or proliferative changes have taken place. The effect on the kidney function is obvious. There is no glomerular filtration, no filtrate for the tubules to concentrate and there are changes in the composition and volume of the blood due to the accumulation of water and nitrogenous waste products in the blood. The total non-protein nitrogen, the urea, uric acid and creatinin which can be determined are found to be increased, the blood is diluted by the water which is not excreted, which can be easily determined by the proportionate fall of the red cells and hemoglobin. If the angiospastic contraction is less intense and if it is overcome to a varying extent, the glomeruli receive some of the blood plasma even though the red cells are not able to enter the capillaries and filtration occurs just to that extent. Concentration by the tubules is effected insofar as they are functionally capable in spite of the degenerative changes in them. Water and nitrogenous waste retention varies with the degree of glomerular permeability to the inflow of plasma and is practically a function of this and of the mechanism which attempts to overcome the angiospastic contraction.

What is this mechanism? Reflex vasoconstriction carries with it an attempt to remedy the vasoconstriction. One would naturally conclude that to overcome obstruction to blood flow, increased pressure above the seat of the obstruction would be the remedy. We mentioned that afferent vasomotor impulses from exposure

of the skin to cold will cause diminution of the urine due to constriction of the renal vessels and at the same time an increase in blood-pressure due to constriction of the splanchnic vessels. It is this increase in blood-pressure which is produced by the mechanism concerned in the production of the angiospastic ischemia, which is the means of overcoming the obstruction to the inflow of the blood into the glomeruli. The ability on the part of the body to maintain this increase in blood-pressure may be little or much at the beginning of the angiospastic contraction, according to the reserve of pressor substances at its command, but as the disease progresses the body evidently acquires the means of maintaining the blood-pressure. Langhans[24] was able to inject the glomeruli in kidneys of acute nephritis with Prussian blue, but with a much increased pressure. Huelse[25] was able to inject the glomeruli of three cases of nephritis with practically the same pressure which these cases presented during their illness. That the increase in blood-pressure in diffuse glomerulo-nephritis, which may be maximal, is just for the purpose of overcoming this resistance to filtration is apparent when we consider that without this increase in pressure filtration by the glomeruli becomes impossible.

We do not know the entire mechanism for the maintenance of the increased blood-pressure. Volhard[26] assumes, and with reason, that the reflex stimulation of the splanchnic nerves, which causes increase in blood-pressure by constriction of the splanchnic vessels, causes at the same time an increase in the production of adrenalin. He also assumes that the afferent impulses from the nerves of the renal vessels stimulate the vasomotor center or the splanchnic nerves direct with an increased output of adrenalin. The inability to find an increased amount of adrenalin in the blood is not against this, as the adrenalin is continuously used up at the seat of its activity.

How can we explain the clinical phenomena on the basis of the glomerular ischemia?

It is not the purpose of this paper to discuss every possible symptom of nephritis, but the essential clinical phenomena of the various forms of diffuse glomerulo-nephritis. This disease, as we have said before, has always its origin in an acute form, and, according to Volhard's theory, in an acute angiospastic ischemia. It may also appear without the obvious symptoms and so remain unnoticed by the patient who has, therefore, at a later stage, no recollection of the acute beginning.

The essential clinical phenomena of the acute stage of diffuse glomerulo-nephritis are: (1) The urinary changes, of which hematuria is the distinctive feature, with albumin and casts; (2) the edema; (3) the increase in blood-pressure; (4) the changes in the blood; (5) as a complication, the phenomena, especially of the nervous system, which go by the name of uremia.

The angiospastic obstruction to the inflow of blood into the glomeruli carries with it, as we have discussed above, the immediate consequence of oliguria, compensatory increase in blood-pressure and changes in the composition of the blood. These three phenomena are always functional variables of the intensity and duration of the bloodlessness. The *hematuria* has probably several sources. Owing to the bloodlessness of the glomeruli there is an increased filling and back pressure in the venous system of the kidney with engorged intertubular capillaries with rupture. A second source is the rupture of the first divisions of the vasa afferentia of those glomeruli which have already become permeable to the entrance of blood. A third source is the exudation of blood through the capillaries around the glomerular capsule. The albuminuria is not a distinctive feature, as it is common to all forms of nephropathies. Undoubtedly some of it is due to the increased permeability of the glomerular membrane as a result of the ischemia; some may also come by way of the tubules. We have no definite knowledge about this.

The *edema* of acute diffuse glomerulo-nephritis is general and the edema fluid differs in composition from the edema of cardiac failure as well as from the edema of nephrosis. It is characterized by relatively high protein content and is practically a filtered plasma. Beckman[27] in examining fluids of all the three varieties of edema found the highest protein content in the edema fluid of acute glomerulo-nephritis. The production of this form of edema is best explained by filtration through the capillaries. The factors which cause the acute angiospastic contraction in the kidney is also responsible for the angiospastic contraction of the small vessels and capillaries in the skin. Weiss[28] observed, with his new method, the skin capillaries in a case of nephritis following a cold. He found the capillaries tortuous, the blood flow slow and granular. We must assume that there is an increased pressure in the capillaries with filtration or possibly a lessened nutrition of the capillaries with a consequent increased permeability of their walls.

The *increase in blood-pressure* we have attempted to explain. In the acute cases an increase of 30 to 50 mm. of mercury is usual. It rarely goes above 180, and the dropping of the previously increased blood-pressure in acute nephritis is one of the first indications that the glomeruli are returning to normal.

The *changes in the blood*, namely the increase in the blood of water and nitrogenous waste products, are purely a function of the glomerular ischemia and vary with it, and vary inversely with the blood-pressure insofar as the blood-pressure is able to overcome the ischemia and cause filtration.

The uremia we shall discuss later.

In discussing the pathologic histology we have spoken of four directions in which the process of acute diffuse nephritis may pro-

ceed. We have said that the first possibility is that the glomeruli again become permeable to the entrance of blood and return to normal. Clinically, this means that the acute nephritis is cured. That acute diffuse glomerulo-nephritis is curable forms a part of our understanding of the disease, and it is curable as long as the changes in the glomeruli have not advanced beyond those which we have described under the heading of the acute form.

The clinical phenomena of the subacute, subchronic and chronic forms have this in common, in that they all show the phenomena of renal insufficiency, with an increase in blood-pressure to overcome the resistance to the entrance of blood into the glomeruli.

The subacute form is characterized by a subsidence of the acute symptoms, especially the hematuria, and often by the subsidence of the edema. The increase in blood-pressure persists and is dependent upon the ability of the body to produce pressor substances, especially adrenalin. Whatever filtration is possible is dependent upon the increase in pressure, and with the fall in pressure the renal insufficiency increases to a maximum. The waste substances in the blood increase proportionately, and death is due to renal insufficiency or at times to an acute convulsive seizure.

The subchronic form is characterized clinically by the persistence of the hypertension after the disappearance of the acute symptoms. The kidney at first assumes more of its function with the increase in the pressure, but gradually renal insufficiency develops. This form may run without edema, but it is just in this form that there is often marked fatty and lipoid degeneration in the tubules with a corresponding edema and marked albuminuria. These cases of the subchronic form Volhard calls "nephritis mit nephrotischem Einschlag." They are the mixed cases in which Epstein[29] found, in addition to the hypertension, the phenomena of nephrosis, an increase in the cholesterol of the blood, reduction of the blood protein, and an inversion of the albumin-globulin ratio. As a result of the hypertension there is cardiac hypertrophy. Termination of these cases is usually from renal insufficiency which results from the inability of the hypertension to overcome resistance to the entrance of blood into the glomeruli. Renal insufficiency may also result from the fall in blood-pressure due either to the failure on the part of the body to supply sufficient pressor substances, or to cardiac failure as a result of excessive demand on the heart by the increase in blood-pressure.

The very chronic or endarteritic form presents phenomena which are more complex. The duration is many years. The acute stage may have been severe or so mild that the patient does not remember it. The acute stage subsides, the blood-pressure returns to normal and only the continual presence of albumin in the urine may remain. The angiospastic renal ischemia has been relieved and the glomeruli again obtain the full supply of blood.

But here as a result of the ischemia changes in the smaller vessels have developed with thickening of the intima which shows in places degenerative changes. These changes are permanent and are of the character of an obliterating endarteritis. The lumen gradually becomes narrowed, and here and there some vessel becomes obliterated. This results again in an ischemia of some glomeruli, but as these changes in the vessels are organic and permanent, the glomeruli which are supplied by these vessels become entirely obliterated. The process is a slow one, and for many years the gradual reduction in the number of the glomeruli, although it affects the kidney reserve, does not produce any clinical phenomena. That the reserve is reduced often becomes manifest when the patient notices that after drinking heavily elimination of water is not so prompt and he has to get up at night, although this is not necessary on his ordinary fluid intake. Transient rises of blood-pressure occur at such times with an increased water content of the blood.

With the gradual reduction in the number of the glomeruli as a result of the obliterating endarteritis, the lumen of the smaller vessels which supply the rest of the glomeruli becomes narrowed to a degree that threatens the maintainence of normal blood-pressure of these glomeruli. A certain height of blood-pressure must be maintained in the glomeruli if filtration is to occur. Experimentally, it has been shown that urine production ceases at a blood-pressure of about 40 to 45 mm. of mercury. For normal filtration a much higher pressure is necessary, and the pressure in the glomeruli normally is probably very little lower than that of the aortic pressure. We know that in Addison's disease when the blood-pressure sinks permanently to 75 or 80 mm. of mercury, functional renal insufficiency becomes evident from the increase in the blood of the waste products of metabolism.

The result of the narrowing of the arterioles is an increase in blood-pressure, which gradually increases as the lumen of these vessels becomes more and more narrowed by the changes in their walls, and as more of the glomeruli are destroyed as a result of the obliteration of these vessels. The hypertension is compensatory with the object of maintaining filtration pressure in the glomeruli. It is effected here by reflex vasoconstriction of the entire peripheral vascular system. Reflex impulses from the diseased arteries cause the vasoconstriction, and with the reflex stimulation of the splanchnic nerves, an increased output of adrenalin which persistently maintains the vasoconstriction. The evidence for the generalized peripheral vascular constriction can be found by observing the skin capillaries according to modern methods, and better still, by observing the vessels of the retina with the ophthalmoscope. These show at this stage constriction of the arteries and after a time, as a result of the ischemia, areas of degeneration with lipoid deposits.

We have then as the clinical expression of the very chronic form, at first a period of complete absence of any indication of renal disease with the exception, possibly, of a persistent albuminuria. This is followed by a second period characterized by a gradually increasing hypertension with a gradual diminution in the kidney reserve. The hypertension is often very high and the whole second period, which may last for many years, may present nothing else but this hypertension. As a result of the high blood-pressure, there is cardiac hypertrophy, and at times headache is complained of. Kidney reserve is diminished. This may be tested by giving a single large quantity of water, when it will be found that elimination is not prompt and is prolonged over a longer period of time than normal. The intake of a measured quantity of protein, or of urea, will cause a greater than normal increase of urea in the blood, and the increase will remain longer, indicating that elimination is prolonged. With the reduction in the number of the glomeruli there is also a loss of the corresponding tubules, and therefore, a lessening of concentration which is evident from the lower specific gravity of the urine. As absorption in the tubules is diminished, larger quantities of urine must be eliminated, but the urine is dilute and more nearly approaches the glomerular filtrate.

This second period of chronic glomerulo-nephritis so commonly presents only hypertension that it is often indistinguishable from the essential or benign hypertension of renal arteriosclerosis, the nephrocirrhosis arteriolosclerotica (Ashoff). In the benign sclerosis there is also a gradual narrowing of the smaller vessels, but this is due, not to an obliterating endarteritis following an acute ischemia, but to a true arteriosclerosis of the smaller vessels. The process is much slower, the patient usually older, there is no history of a previous acute nephritis, and, as this is the main point, the functional reserve of the kidney is much less, or not at all, disturbed. The symptoms are mainly cardiac and arterial, and not renal. In some cases occurring in younger individuals differentiation may be difficult.

Both diseases, the benign arteriosclerosis of the kidney and the second period of chronic glomerulo-nephritis, are often spoken of together as focal nephrosclerosis. This name only expresses the histological picture and lays emphasis on the areas of connective tissue growth which are really only the burial grounds of the glomeruli. It does not express what is really the main thing, that it is the changes in the vessel wall and the narrowing of the lumen which are responsible for the compensatory increase of blood-pressure, and that it is the ability of the rest of the glomeruli to filter or not, and of the tubules to concentrate or not, which is responsible for the variations in the kidney reserve function. Nor does this name express whether the clinical picture is that of the benign arteriosclerosis or of the progressive second stage of chronic nephritis.

During the second period of the chronic form there occur attacks of acute ischemia, such as are responsible for the beginning of the disease. These attacks have the same pathogenesis and probably the same ultimate cause. The kidney, once the seat of an acute ischemia, seems predisposed to its recurrence. The acute ischemia adds its symptoms to the chronic symptoms, and as far as the symptoms are due to the acute process they are retrogressive. It often happens that a patient with a history of an acute beginning, and in whom the gradual development of hypertension has been followed, is taken sick with edema, an enormous increase in the blood nitrogenous waste products, with hematuria and albuminuria. This subsides under rest and treatment, and credit is then claimed for the form of treatment employed in curing a supposedly chronic nephritis. When we realize that only the acute forms are retrogressive, and that the clinical phenomena of chronic glomerulo-nephritis is due to permanent organic changes in the vessels and the glomeruli, which cannot, by their very nature, retrogress, we must also realize how little we can claim for any treatment from which we expect to widen the narrowed lumen of vessels or bring to life obliterated glomeruli.

The third stage of the chronic form of glomerulo-nephritis appears when the changes in the vessels of the glomeruli have progressed to a stage where, despite increased pressure, and despite maximal efficiency of the remaining glomeruli, kidney function cannot be maintained. The "kidney rest," as some express it, is unable to maintain normal function even on a low food and water intake, and kidney reserve has entirely disappeared. Clinically, this expresses itself in the phenomena of renal insufficiency. Blood-pressure is very high, usually above 200. When this sinks and remains low, the degree of renal insufficiency is increased. The evidence for a prolonged contraction of the peripheral vessels is found in the eye grounds. Especially the radiating star-shaped white lines around the macula represent degenerated areas where the vessels have become obliterated.

The renal insufficiency manifests itself in the changes of the composition of the blood, in diminished glomerular filtration and diminished concentration by the tubules. The glomeruli are enlarged, but small in number, and are working with maximum efficiency. In spite of this they are unable to filter the excess of waste products from the blood, and we have, therefore, a gradual accumulation of water and these waste substances in the blood. The water increase in the blood can best be determined by counting the red corpuscles and by determining the hemoglobin. Both are found to be reduced in proportion. The anemia which is thus found does not represent the real loss of blood elements, but represents a dilution of the blood; a true hydremia. The color index is usually around one, and there is no evidence of either

blood regeneration or blood destruction. Occasionally bleeding from the mucous membranes adds to the degree of the anemia. The anemia occurring in nephritis has been recently investigated by B. N. Berg in the wards of the Mt. Sinai Hospital.

The following figures represent the blood composition of a man aged thirty-six years who had an acute glomerulo-nephritis at the age of twelve, several recurrent attacks, the last one at the age of twenty-six, with a gradual increasing hypertension. A week before his death his systolic blood-pressure was 230 mm. of mercury, and his diastolic 140. At that time his blood figures were as follows:

Hemoglobin	54
Red corpuscles	2,500,000
Platelets	110,000
White blood cells	16,000
Polymorphonuclears	91 per cent
Incoagulable nitrogen	151.2 mgm. per 100 cc
Urea nitrogen	270.0 " " "
Uric acid	6.5 " " "
Creatinine	21.0 " " "

The figures of the blood elements represent practically a dilution to half, with a marked leukocytosis. The figures for the nitrogenous waste products are exceedingly high.

As the remaining normal glomeruli filter with maximal efficiency in response to the diluted blood, and as the tubules concentrate maximally, a practically constant quantity of urine is produced which does not vary with the fluid intake. In the case mentioned there was a constant production of urine of about 30 cc per hour or about 720 cc in twenty-four hours. The urine was of a fixed specific gravity of 1010, of light color and containing a small amount of albumin. It is often said that the water elimination in these cases is normal, and the fact that the patient can pass three-fourths of a liter of urine in twenty-four hours, would seem to indicate that such is the case. This is misleading. We have to consider that normally many liters of the glomerular filtrate must pass through the tubules to be concentrated to produce one liter of normal urine (Cushny). In a case like the one above, the urine is only very slightly concentrated above that of the glomerular filtrate. Yet, instead of the many liters that should be passed because of this lack of concentration, granted water filtration were really normal and concentration alone impaired, we have only 720 cc of a dilute urine, probably very closely resembling the glomerular filtrate.

The course of this third or final period is dependent upon the rapidity with which the glomeruli become obliterated, upon the maintenence of the hypertension, upon the cardiac sufficiency. Edema is not an essential part, but occurs at times with the fall in blood-pressure, and also from myocardial insufficiency.

Death is due to uremia. In this, the chronic form, we mean that it is due to poisoning of the system by the retained waste products, especially urea. We have said before that uremia also occurs as a complication in the acute diffuse glomerulo-nephritis. What then is meant by uremia? Definition is difficult, and we shall not attempt it. We mean by it certain phenomena which occur in the course of the various forms of nephritis, which are especially the results of cerebral involvement. We accept Volhard's division of uremia into, (1) true chronic uremia; (2) chronic pseudouremia; (3) acute convulsive or eclamptic uremia.

True chronic uremia is due to the prolonged retention of the nitrogenous waste products, and always expresses the clinical end stage of chronic nephritis. It is characterized by a gradually increasing fatigue and drowsiness combined with irritation phenomena. There is tremor of the extremities, sudden contraction of muscles, tendon jumping, the normal reflexes are increased, but there are no abnormal reflexes, such as a Babinski. There is a loss of flesh which was thought by Senator to be due to a toxic destruction of protein, and was produced experimentally by Bradford, by the reduction of the kidney tissue to one-fourth its volume. This loss of flesh is probably due to the increased metabolism as a result of the dynamic action of the amino acids of the blood, which are also increased. There are also disturbances of the gastro-intestinal tract, such as loss of appetite, singultus, vomiting, diarrhea, stomatitis, gastritis, and enteritis, with urinary fetor *ex ore*. Due to the retained acid phosphate salts there is diminution of the alkali reserve in the blood, resulting in a slow and deep breathing sometimes periodic in character, and which is characteristic of states of acidosis. Pericarditis is a common occurrence. Before death there is usually a fall in temperature. Convulsive seizures are not part of the essential picture of true uremia, and although occasionally convulsions do occur, more often they do not.

The symptoms of pseudouremia occur in the course of prolonged hypertension. They are not due to retained waste products and occur in the second period of chronic nephritis, but more often with the hypertension of the benign kidney ateriosclerosis or arteriolosclerosis. They are arterial in character, and due to sudden temporary angiospastic ischemia in the different organs, especially in the brain. Depending upon the location there occur transitory paralyses, aphasia, epileptoid phenomena, bulbar symptoms, Cheyne-Stokes breathing, and others. Osler[39] describes such classical cases.

The acute convulsive or eclamptic uremia occurs occasionally in the end stage of chronic nephritis, but its typical occurrence is more commonly a complication in the course of acute diffuse glomerulo-nephritis. It is not an essential part of the clinical picture, and the course of an acute diffuse nephritis may run entirely

without any convulsions. It is characterized by the classical epileptiform attack with coma, or some equivalent form such as headache, restlessness, vomiting, unconsciousness, blindness. The convulsions are sometimes tonic, more often clonic, occasionally only on one side and with or without an aura. There are psychic equivalents ranging from fits of depression to maniacal conditions. The headache, vomiting, slowing of the pulse and choked disk may simulate a brain tumor. Lumbar puncture relieves and often stops the convulsions.

In explaining the pathogenesis of convulsive uremia occurring as a complication in acute diffuse glomerulo-nephritis, Volhard assumes that the angiospastic contraction, which is general, occurs also in the brain. The angiospastic contraction of the peripheral blood vessels results in edema due to filtration through the capillaries or to increased permeability of the capillaries, as a result of disturbances in their nutrition. The same process occurs also in the brain, resulting in an edema of the brain. The brain swells and is compressed in the rigid cranium with consequent irritation of the cortex. This is aided by the added increase in blood-pressure which always precedes the convulsive attack. He quotes Loeschke as showing that when death results from convulsive uremia, the brain when properly cut *in situ* snugly fits the walls of the skull, and the ventricles of the brain show themselves as linear slits. This explanation leans on the old Traube theory of swelling of the brain. It is more reasonable and more in accord with the pathogenesis of diffuse nephritis than the hypothetical poisonous irritant assumed by many investigators.

Conclusions. Volhard's theory of acute angiospastic renal ischemia as the starting point of diffused glomerulo-nephritis is the best explanation so far offered for the pathogenesis of this disease. We have attempted to follow the consequences of such an ischemia on the kidney function of filtration and concentration and on its function in helping to maintain the constancy of the volume and composition of the blood. We have also attempted to follow the changes occurring in the kidney following the angiospastic ischemia, and to explain the clinical phenomena on the basis of such changes. The theory is also of value in the treatment of this disease. We must realize that our efforts can only be directed toward those changes which are still retrogressive. When these changes have passed on to a stage where they are no longer retrogressive, treatment can only be directed toward lessening the functional load of the kidney. At all times where the functional reserve of the kidney is lessened or has entirely disappeared, either by acute ischemic or by chronic changes, treatment should be directed toward limiting the intake of those substances which in their normal quantities cannot be eliminated by the kidney which has become limited in its function. These substances are protein

food and water, and their reduction is always indicated when the blood shows an increase in the nitrogenous waste substances.

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STUDIES OF GRAVES' SYNDROME AND THE INVOLUNTARY NERVOUS SYSTEM.*

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General Introduction. These studies result from an attempt to promulgate a definite policy for the management of individuals

* These studies were carried on in the Medical Department of the Mt. Sinai Hospital and in the Department of Pharmacology of the College of Physicians and Surgeons, Columbia University. The work has been made possible by a fund established for the purpose by the New York Foundation and by Mr. Felix Warburg. The basal metabolism readings throughout were made by Dr. Herman Lande to whom we are indebted for his painstaking, accurate and conscientious work.

suffering from Graves' syndrome. In our hospital this condition has been handled by the surgeons, internists and radiotherapists. Each group has reported successful results, not only in those patients who had received no previous treatment, but also where other treatments had proved a failure. For two reasons it was impossible to compare or estimate therapeutic reports: (1) There has been no concordance as to just what constituted Graves' syndrome, and (2) data as to end-results have been meager and subject to individual interpretation.

A survey of the literature failed to clarify the situation. The diagnostic criteria varied; case reports were frequently not supplied; personal opinion and interpretations rather than actual facts were presented; end-results were either obscurely reported in massed statistics or were not given at all. Satisfactory individual records, however, are to be found in the papers of Du Bois[1] and Means and Aub.[2]

One of us (H) visited the leading goiter clinics in 1920 to determine whether more could not be learned from personal observation. While each clinic had its definite plan as to diagnosis and therapy, no two clinics were found with policies that were similar; even in the same institution the widest possible variation obtained among different services.

We decided, therefore, that a small group of patients with fully developed Graves' syndrome† be studied carefully from every angle. In order to eliminate the personal factor it was determined not to include in this group a patient in whom the clinical diagnosis was not confirmed by a distinct and continuous elevation of the basal metabolism. The course of the basal metabolism was accepted as the best available objective[1] criterion of the severity and progress of the disease. The complete data of this group of definite Graves' syndrome are compiled in paper III.[7]

A large number of patients were referred to us who, while they presented many of the cardinal clinical symptoms, *i. e.*, tachycardia, exophthalmos, goiter and tremor, associated with some of the minor symptoms (diarrhea, sweating, palpitation, etc.), nevertheless showed no constant elevation of the basal metabolism, and gave no histories suggestive of a previous crisis. They were studied separately for classification and for the purpose of establishing the differential diagnosis from Graves' syndrome. Of these the first subgroup was composed of patients who had an enlargement of the neck. They had no other manifestations of Graves' syndrome, and no elevation of the basal metabolism. It became apparent that these patients were suffering: (1) From an existing hyperplasia

† For its historical interest we have retained the term "Graves' Syndrome." The introduction of basal metabolic studies has thrown new light on the syndrome, and we have altered our conception in accordance, as will be seen from the text.

of the thyroid gland; (2) from the results of a previous hyperplasia, (3) from adenoma. A review of the etiology, physiology and clinical associations of hyperplasia and adenoma, with the case reports in this subgroup, form the basis for paper I. In a second subgroup were patients, who, with or without goiter, exhibited many of the classical manifestations of Graves' syndrome. In these there was no significant elevation of the basal metabolism and no reason to believe that an elevation had ever existed. Their manifestations were clinically divisible into three groups: (1) The registration in consciousness of somatic activities which normally proceed unconsciously, as palpitation; (2) objective functional disorders in organs which themselves were apparently healthy (tachycardia, diarrhea); (3) symptoms of obscure origin which were accentuated by the administration of adrenalin (tremor, asthenia). With the possible exception of thyroid enlargement, all of these symptoms and signs were sympathomimetic.‡ To these clinical disturbances of the involuntary nervous system we have applied the term *Autonomic Imbalance*. The clinical study of patients with autonomic imbalance is presented in paper II.[3]

Because the symptoms of Graves' syndrome and autonomic imbalance were found to be due to disturbance in the realm of the involuntary innervation we studied the physiology and pharmacology of the involuntary nervous system.

We do not claim that either Graves' syndrome or autonomic Imbalance is necessarily an inherent derangement of the involuntary nervous system, but that whatever the ultimate cause it must operate either primarily or secondarily through the involuntary nervous system. The attempt to find an index for the activity of the involuntary nervous system is described in paper IV.[4] By means of this index, the role of alleged etiologic and therapeutic influences, as well as factors which maintain the tonicity of this system, were investigated. These results are presented in papers V, VI and VII.[4]

Finally, a definite therapeutic policy for Graves' syndrome was sought. In a disease where "specific" results have been claimed for general medical treatment; for tonsillectomy; for roentgen-ray exposures of thyroid or thymus, or both; for mechanotherapy; for spondylotherapy; for surgery, from injections to ligations, and from partial to subtotal thyroidectomy; for endocrinology,—the suspicion was aroused that there was a "nonspecific" factor common to all these "cures" and that the course of the disease was toward spontaneous arrest. Accordingly we studied fifty patients (Paper III) with Graves' syndrome without employing "specific" measures, in

‡ Adopting the term of Barger and Dale[2] to denote manifestations that are tantamount to electrical stimulation of the thoracico-lumbar division of the involuntary nervous system, or to stimulation of the same system by adrenalin.

order to determine its natural history as an index for the evaluation of therapeutic procedures.[6]

A general summary of the clinical and laboratory work on the involuntary nervous system constitutes paper VIII[5], and a discussion of the pathogenesis and an evaluation of popular therapeutic procedures constitutes paper IX.[6]

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STUDIES OF GRAVES' SYNDROME AND THE INVOLUNTARY NERVOUS SYSTEM.

I. Thyroid Enlargement in Individuals Without Sympathomimetic Manifestations.

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Studies on the condition of thyroid enlargement are usually made in lake districts where goiter is endemic, and consist of massed statistical reports.[1] The great frequency of endemic goiter has obscured the study of thyroid enlargements due to other causes.

Our work was done at a seaport where thyroid enlargement is relatively infrequent. An out-patient department was organized and an attempt made to determine the etiological factor in the individual patient. The conditions associated with and resulting from the thyroid enlargement were studied with the object of investigating the possible relationship between goiter and Graves' syndrome.

Of over 200 patients investigated, 55 furnished material for this paper. Of these, 32 patients (Table I) presented as their sole symptoms the "lump in the neck." The other 23 patients (Table II) had, beside thyroid enlargement, some other unrelated disease which was responsible for the presenting symptoms.

TABLE I.—THYROID ENLARGEMENT IN INDIVIDUALS FREE FROM SYMPATHOMIMETIC SYMPTOMS AND WITH NORMAL BASAL METABOLISM.

No.	Sex.	Age	Age onset goiter.	Duration of goiter.	Previous treatment.	Tonsils.	Miscellaneous.	Effect of iodide.
8673	F.	43	?	?	None	Infected	Calcification	
8545	F.	36	?	?	25 roentgen-ray	.....	Small adenoma referred as exop. goiter	
8543	F.	56	44	12	Roentgen-ray	.....	Referred as exop. goiter	
5066	M.	33	21	12	Roentgen-ray	Infected		
9234	F.	14	12	2	Chiropractor	.....	Puberty hyperplasia	
9080	F.	50	26	24	.....	.....	Regarded as exop. goiter (?)	
8651	F.	50	?	?	.....	Infected	Referred as exop. goiter	
9220	F.	33	?	?	.....	.....	Discrete tumor	
9198	F.	34	19	15	.....	.....	Referred as exop. goiter	
8718	F.	30	30	5 wks.	.....	.....	Discrete tumor	3 cm. 5 mos.
8803	F.	26	?	?	.....	.....	Discrete tumor; removed for relief of cough. Still coughs	
9215	F.	37	34	3	.....	.....	Referred as exop. goiter	
9125	F.	18	15	3	Ops. 2 yrs. ago	.....	Gland still enlarged	
8891	F.	36	36	1 mo.	.....	.....	Discrete tumor	8 cm. 6 mos.
8766	F.	29	?	?	Injections into gland	.....	Referred as exop. goiter	
8517	F.	26	?	?	.....	.....	Referred as exop. goiter	
8581	F.	30	?	?	.....	.....	Referred as exop. goiter	3 cm. 10 mos.
8748	F.	29	25	4	.....	Infected	Puberty hyperplasia	
8681	F.	14	11	3	.....	.....	Puberty and starvation	
8963	F.	30	?	?	.....	Infected	Referred as exop. goiter	2 cm. 4 mos.
8760	F.	18	8	10	.....	.....	Referred as exop. goiter	3 cm. 8 mos.
8869	F.	23	?	?	.....	Infected		
9157	F.	18	16	2	.....	Infected		
8863	F.	38	34	4	.....	Infected	Thyroid exhaustion (?)	7 cm. 6 mos.
9193	F.	28	11	7	Ops.	.....	Post-partum; increased after ops.	
8734	F.	47	44	3	.....	.....	.....	5 cm. 6 mos.
8882	F.	19	19	2 mos.	.....	.....	.....	2.5 cm. 3 mos.
8674	F.	19	15	4	30 roentgen-ray	.....	.....	3 cm. 9 mos.
9194	F.	30	?	?	.....	.....	.....	3 cm. 1 mo.
8606	F.	50	?	?	.....	.....	Referred as exop. goiter	
8599	F.	43	?	?	.....	.....	Referred as exop. goiter	
8832	F.	42	?	?	.....	.....	Referred as exop. goiter	

CHART 1.—Note wide variation in age at time of admission; variation in age of onset of goiter and in duration of goiter; roentgen-ray fails to shrink goiter; compensatory hyperplasia after operation; 8 have infected tonsils; character of goiter varies some diffuse and others discreter preponderance of females; shrinkage with iodide; 14 referred as exophthalmic goiter.

Clinical Data. *Sex and Age.* Fifty-two of the 55 patients were females. The ages of the patients were between fourteen and fifty-six. The two extremes at which the goiter was first noted were also

at fourteen and fifty-six years, and the duration up to the time of admission varied between one month and twenty-four years.

TABLE II.—THYROID ENLARGEMENT IN INDIVIDUALS WHO ARE SUFFERING FROM ANOTHER BUT UNRELATED DISEASE AND WHO HAVE NEITHER SYMPATHOMIMETIC SYMPTOMS NOR ELEVATION OF BASAL METABOLISM.

No.	Sex.	Age.	Thyroid.	Associated condition.	Miscellaneous.
5144	M.	32	Cyst	Tuberculosis (healed); anxiety neurosis	Referred as exop. goiter.
9219	F.	25	Removed in 2 ops.	Manic-depressive psychosis	Ops. as exop. goiter.
8515	F.	50	Diffuse	Diabetes mellitus	
8535	F.	42	Cyst	Anxiety neurosis	Referred as exop. goiter.
8679	F.	59	Diffuse	Diabetes mellitus	
5619	M.	70	Substernal	Myocarditis, emphysema; chr. bronchitis	Cough supposed to be due to thyroid.
8854	F.	33	Diffuse	Anxiety neurosis	Referred as exop. goiter.
8501	F.	47	Diffuse	Chronic hypertensive nephritis; prominent eyes	" " "
9214	F.	?	Diffuse	Fainting spells	Referred as exop. goiter.
8650	F.	29	"	Asthenia after flu.	" " "
8600	F.	14	"	Myositis, infected tonsils	" " "
8585	F.	20	"	Sinusitis	" " "
8580	F.	37	"	Pregnancy	" " "
8542	F.	46	"	Gastric symptoms	" " "
				Infected tonsils and sinusitis	Had roentgen-ray therapy.
8548	F.	34	"	Polyarthritis	Referred as exop. goiter.
8925	F.	29	"	Cystorectocele	" " "
8660	F.	24	"	Psychoneurosis	" " "
8661	F.	16	"	Dysmenorrhea	" " "
8743	F.	43	"	Cholelithiasis	" " "
8922	F.	26	"	Sterility, infantile uterus	" " "
8824	F.	34	"	Mitral stenosis	" " "
8560	F.	40	"	Diabetes mellitus	" " "
8532	F.	38	"	Cancer of uterus	" " "

Note tendency to attribute to thyroid rather than other obvious associated condition the presenting symptoms.

Etiology. In many of the patients the etiological factor could not be determined, because they were not at all sure as to the time of appearance of the goiter. The relationship to puberty and to the child-bearing period was definite in 13. Infected tonsils were present in 8. In one girl the goiter was apparently congenital.

Symptoms. In the first group (Table I) the only symptom was the thyroid enlargement. In the second group (Table II) presenting symptoms were due to a great variety of associated conditions, one each; cancer of the uterus, cholelithiasis, mitral stenosis, cystorectocele, pansinusitis, diabetes mellitus, arthritis, pregnancy, chronic nephritis, generalized atherosclerosis and infantile uterus and neuroses in 6. One woman suffered from a manic-depressive psychosis.

Diagnosis. Of the 32 patients listed in Table I at least 17 were referred with the diagnosis of exophthalmic goiter. In many others the presumption is strong that this diagnosis had been made by the attending physician. Four had received frequent roentgen-ray

exposures and 3 had been subjected to operations on the thyroid gland. Of these 1 suffered a compensatory hyperplasia, so that the gland is now larger than prior to operation.

Of the patients recorded in Table II, practically all were referred to us as examples of exophthalmic goiter and in almost all there was supposed to be a definite connection between the associated conditions already mentioned and the thyroid enlargement. The patient with the manic-depressive psychosis had had thyroidectomy twice without any effect upon her condition. Three had had unsuccessful treatment of the thyroid gland with frequent roentgen-ray exposures. Except for the goiter none of the individuals in either group had had at any time evidences of any of the manifestations of Graves' syndrome. None presented metabolic disturbances as measured by the basal metabolism.

The Type of Gland. From clinical examination it was impossible to determine the pathological type of thyroid enlargement. In no instance was opportunity for histological examination afforded. This, however, is of little importance, because in those glands that were uniformly enlarged a colloidal or hyperplastic picture must have been present at the time of examination. In either instance it may be assumed that the patient had passed through a stage of hyperplasia [3] [4] without sympathomimetic manifestations.

In 6 individuals the enlargement was due to the presence of a discrete nodule, presumably an adenoma. No symptoms accompanied this enlargement. In 2 patients the goiter was substernal.

Treatment. All these patients received small doses of syrup of the iodide of iron,[5] 10 to 30 drops twice a day. The majority of these patients were referred to us merely for diagnosis and no attempt was made to follow them. Of the 11 who were followed not one failed to show a definite softening and decrease in the size of the gland as a result of the iodine administration. On the average the shrinkage in the circumference of the neck was 1 cm. a month. Seven had had treatment by roentgen-ray before being referred to us, and none of these patients reported diminution in the size of the goiter as the result of the exposures. Four had had thyroidectomy. Of these, 2 still had thyroid enlargement; 1 had such a marked compensatory hyperplasia that the gland was actually larger than it had been before operation. In the remaining 2 the gland was definitely smaller; however, in both of these latter patients the operation had been done not for the cosmetic effect but for the relief of cough in the one and manic-depressive psychosis in the other. Neither of these conditions was affected.

Discussion. 1. ARCHITECTURE OF THE THYROID GLAND. There are two special pathological conditions that give rise to uniform enlargement of the thyroid gland. These have been described by Marine[6] in his classical article in which he recognized as ground

types; the normal, the hyperplastic, and the colloid gland. The histology of the normal gland is familiar. The hyperplastic gland differs in that the epithelium is higher, the colloid is less, the walls of the alveoli may be thrown up into plications, the intercellular substance and the vascularity are increased, and there may be round cell infiltration of the stroma. The colloid gland presents large amounts of colloid material, distending alveolar spaces, a flattened epithelium and relatively enormous thickening of the walls of the bloodvessels. In each type variations in intensity may be present. Transitional forms are also observed, in which there is evidence of hyperplasia in a colloid gland, and *vice versa*. There may be present, particularly in the colloid type, secondary changes such as cyst formation, hemorrhage and calcification, which are accidental.

Discrete enlargements of the thyroid gland are due to cysts or adenomata. The latter may present the same alterations as the non-tumor tissue, so that the adenoma may resemble normal, colloid or hyperplastic thyroid tissue. The non-tumor tissue of the gland is not necessarily of the same architecture[7] as the adenomata.

2. The Chemistry of the Thyroid Gland. Investigation of the chemistry, particularly of the iodine metabolism, clarifies the otherwise inexplicable mechanism of the ground types.

Of all the tissues of the body, the thyroid gland alone contains iodine in appreciable quantity. Given by any route or in any form, iodine is quickly bound by the thyroid.[8,9] The iodine content of the normal gland is 1 mg. per gram of dried tissue.[10] The potency of a thyroid extract is directly proportionate to its iodine content. Because of its increased weight the total iodine content of colloid glands either equals or exceeds that of the normal gland. The hyperplastic gland always contains less than 1 mg. of iodine per gram of dried tissue. The total quantity of iodine is always less than in the normal or the colloid gland, and the iodine content is inversely proportional to the degree of the hyperplasia.

The problem of determining whether the architecture depends upon the chemistry or the chemistry upon the architecture, has been definitely solved by the work of Marine.[3] In animals whose glands are rendered hyperplastic, the administration of iodides invariably produces an involution to colloid, but never a resumption of the normal architecture. If iodides are now withheld and the factors producing the hyperplasia remain operative, hyperplasia is reinduced. The resumption of iodides again changes the hyperplastic to the colloid form. From this it must be quite clear that the architecture of the thyroid gland is bound up with the iodine content; that the hyperplastic gland presents a low iodine content, and that the colloid gland has a relative and absolute iodine content that is at least normal: that the colloid gland has passed through a stage of diminished iodine storage. The histological appearance and

chemical examination of the gland merely give information regarding the question of the storage of iodine. Whether the lowered content in the hyperplastic gland is due to: (1) An increased demand for iodine by the body; (2) a decreased supply; (3) an inability on the part of the gland to store iodine, or (4) a modification of the circulating iodine itself, cannot be determined from these examinations. Functionally and in its iodine content the colloid gland departs in in no way from the normal. A gland that is colloid must at one time have gone through a period of hyperplasia. No gland that has undergone any degree of hyperplasia can ever resume its normal appearance.

The hyperplastic gland is therefore the only important structural variation. Until the secretion of the thyroid gland can be accurately measured, no statement regarding the relationship between function and morphology can rise beyond the realm of speculation.

The adenomatous tissue has always less avidity for iodine than the non-tumor tissue of the same gland.[11] In other words, iodine will be bound by the non-tumor tissue before the tumor grasps it, and alterations in the morphology of the tumor are not affected by the iodine until the non-tumor tissue has responded. This suggests that while the iodine metabolism of tumor tissue is qualitatively the same as that of non-tumor tissue, quantitatively it is less active.

3. The Etiology of Thyroid Hyperplasia. Hyperplasia of the thyroid gland occurs as the result of many dissimilar conditions: low iodine intake, the ingestion of polluted water,[12] alterations in the activity of the sex apparatus,[17] after partial thyroidectomy, after the ingestion of large quantities of fat,[13] vitamine insufficiency,[13] the drinking of water from glacial strata, hyperplasia of the thyroid of the gravid mother; and it occurs in congenital cretinism, the hairless pig malady,[14,15] and in Graves'[16] syndrome. Whatever the cause, the use of iodine in any form will result in involution to the colloid type. This strongly suggests that alteration in the iodine metabolism is either a primary or an essential secondary step in the production of hyperplasia by the dissimilar conditions mentioned above.

The architecture of the thyroid gland, in both health and disease, depends therefore upon the iodine economy.

4. The Etiology of Thyroid Adenomata. Thyroid adenomata are seen in congenital cretinism and in many otherwise normal glands. They may show any of the ground types seen in non-tumor thyroid tissue. The fetal adenomata[7] present the most marked degrees of hyperplasia, and the relationship between the histological appearance of the adenoma and the iodine content differs in no way from the relationship in non-tumor tissue. There is no evidence to support a view that the adenomata arise *de novo* in response to an injury, and there is no evidence to show that alterations in the function of an adenoma can occur without altera-

tions in the non-tumor tissue. From the response of the tumor to iodine and from the results of feeding tumor, it is much more likely that in the same gland the tumor is less active than the non-tumor[11] tissue.

5. The Nervous Mechanism of the Thyroid Gland. The nerve supply to the thyroid gland has been demonstrated anatomically. The innervation of the bloodvessels is so abundant that the vascularity of the gland may be most delicately regulated.

The influence of the nerve supply upon the specific secretion of the thyroid gland has not been definitely settled, and about this point has arisen considerable academic controversy. In support of the nervous regulation of secretion the following have been offered: (1) Electrical stimulation[18] of the vago-sympathetic nerves decreases the iodine[19] content; (2) stimulating the vago-sympathetic nerves increases the thyroid secretion as measured by the vascular response to adrenalin;[20] (3) the subcutaneous injection of adrenalin causes an induction current in the gland;[21] (4) continuous stimulation[22] of the nerves, as by phrenico-sympathetic anastomosis, produces a condition resembling Graves' syndrome, which in turn is supposed to be due to hyperthyroidism. In opposition to these there may be offered: (1) Experiments using alteration of iodine content as an index of secretion are complicated by two technical factors (*a*) the iodine distribution in a gland is not uniform[23] and (*b*) the iodine-containing substance may be mechanically squeezed[24] out as a result of the powerful vasoconstriction following nerve stimulation. Again the interpretation of these results is open to the objection that the decrease in the iodine content does not necessarily connote increased secretion, but merely a diminution in the iodine store; (2) we have shown that after stimulating the thoracico-lumbar system with adrenalin[25] the augmented pressor response is due, not to alterations in the thyroid secretion, but to changes in the involuntary nervous system; (3) the production of the induction current may well be due to alterations in the vascular bed rather then in the secretory activity; (4) despite perfect nerve union no changes occur after phrenico-sympathetic anastomosis.[26 27 28]

While the chemical influence on thyroid secretion is so clearly demonstrable and so subtly adjusted it seems quite unnecessary to assign, in the presence of such inconclusive experimental data, more than a minor role to the influences of nervous impulses. Those who hold that the nervous influences control the secretion regard as the augmentor nerve to the thyroid gland the thoracico-lumbar division. If the theory of Gaskell[29] as to the double segmentation of the vertebrate ancestor is correct, then we should expect the augmentor nerve to the endodermal thyroid gland to be bulbo-sacral in origin.

6. Thyroid Hyperplasia and its Effects. In the majority of individuals and in animals in whom thyroid hyperplasia exists,

no extra-thyroidal alterations are constant.[2] In brook-trout[30] and many other animals in which thyroid hyperplasia has been studied, there are evidences in some of increase in weight, diminution in activity, susceptibility to infection, and in mammals a shedding of the hair; in other words, many of the symptoms of myxedema. In the "hairless pig malady,"[14 15] the highest degree of hyperplasia is present and the clinical condition is identical with myxedema. There is little doubt, therefore, that the functional activity of the thyroid may be apparently normal or greatly diminished in the presence of a hyperplasia. The frequency with which hyperplasia occurs in Graves' syndrome has led to the supposition that hyperplasia is an indication of hyperfunction, *i. e.*, a true hyperthyroidism.[31 32] Four facts make this hyperplasia-hyperthyroid theory difficult to maintain: (1) The definite cause and effect relation between the hyperplasia and the marked myxedema in the "hairless pigs;" (2) the association of hyperplasia with almost complete absence of iodine content in human congenital cretinism (myxedema); (3) the low iodine content of hyperplased glands; (4) failure to demonstrate the hormone in the blood from a hyperplased gland even after electrical stimulation of the nerves.

7. Specific Secretion of the Thyroid. The specific secretion of the thyroid is an iodine-containing substance that has been isolated by Kendall[33] and has been named thyroxin.[34] Many other gland extracts have been prepared, most of which are potent, but the compound of Kendall has the advantage of being crystalline, having an exact dosage, a constant chemical composition and it is fit for intravenous injection. As yet no potent compound has been obtained that is free from iodine and the potency of a preparation varies directly with the iodine content. Iodine-poor compounds cannot be made potent by treatment with iodine after or during extraction. Thyroxin is built up by the thyroid cells and stored in the colloid. The synthesis probably takes at least[35] eight to twenty hours. It is secreted into the thyroid veins rather than the lymphatics. Elimination is slow, probably taking forty-eight hours to ten days. Plummer[36] has estimated that the amount circulating is 12 to 14 mgm., or about 1 mgm per 10 pounds of body weight. Allowing the high figure for blood of 10 per cent of body weight, the amount in the blood is 1 mgm. to the pound or a concentration of 1 : 2,200,000. This amount is not detectable by chemical methods and the biological method of Gudersnatch[37] is utilized for the qualitative detection of small amounts. This test relies upon the increase in the rate of metamorphosis in the tadpole when thyroid extract is fed. The iodine content of the thyroid colloid is ordinarily sufficient to be estimated chemically. As has been stated, this varies as the histological appearance of the gland and is normal in normal or colloid glands and adenomata and greatly decreased in general or

local hyperplasia (gland and adenoma). The secretion has been detected in the thyroid veins[38] after electrical stimulation of the vago-sympathetic trunk to a normal gland. Similar stimulation of a hyperplastic gland produced no such effect. This meagre information is all we possess of the estimation of the output from the thyroid and would indicate that the output from a hyperplastic gland, like the storage, is less than the normal and confirms the clinical findings of myxedema associated with hyperplasia. Those who regard hyperplasia as indicating hypersecretion (hyperthyroidism) have difficulty correlating their theory with these findings.

Of the factors that control secretion three have been mentioned: iodine, nervous influences and the circulating epinephrine. Of these the first is potent and delicately adjusted, the second remains unconfirmed and the third is dubious in view of the fact that[38a] we were unable to confirm the data on which the supposition rests even with large amounts of adrenalin. This theory is also opposed by the phylogenetic evidence[29] which would lead one to expect that the stimulation of the thoracico-lumbar division and hence epinephrine would inhibit thyroid secretion.

Reports of feeding experiments with large amounts of thyroid are at variance. At the one extreme are those who claim that all the symptoms of Graves' syndrome including exophthalmos can be reproduced. At the other extreme is Carlson[39] who in an elaborate investigation on various animals and man found loss of weight, gastro-enteritis, and diarrhea as the only symptoms constantly produced. He concludes "It would require considerable imagination or an undue influence of one's wish or of one's judgment to identify the symptom complex of excessive thyroid feeding in experimental animals with exophthalmic goiter." Certain it is that in concentration comparable to that in the circulating blood thyroid extract cannot produce these symptoms. Indeed the effects of small doses indicates a metabolic reversal so that the thyroid is anabolic, and not catabolic. This remarkable finding of Janney[40] emphasizes the need for quantitative studies with thyroid extract. The status of this problem is not unlike that of the question of the function of epinephrin before the quantitative work of Hoskins.[41] It will be remembered that after it was shown that adrenalin elevated blood-pressure it was immediately assumed that epinephrin maintained the vascular tonus. When it was found that the action of adrenalin was reversible[42] and that with small doses vaso-dilatation occurred, Hoskins made quantitative study and found that the concentration of adrenalin necessary to give a pressor effect was also sufficient to cause intestinal inhibition. This experience with adrenalin indicates the fallacy of concluding that the same effects must necessarily be produced by thyroid secretion in the amounts

circulating in the normal economy as are produced by the administration of this substance in large quantities.

The most definite information regarding thyroid effects has been obtained from metabolic studies. On the one hand thyroid feeding increases the heat production in myxedema and on the other hand diminished heat production results from diminution in the thyroid function (ablation, fibrosis or extreme hyperplasia). That the thyroid is not the sole regulator of the heat mechanism is obvious from (1) the fact that the elevation of the basal metabolism caused by adrenalin (stimulation of the thoracico-lumbar division of the involuntary nervous system) is not altered appreciably by thyroidectomy[43] and (2) destruction of the adrenal cortex causes a prolonged and sustained elevation of the basal metabolism in the presence of the thyroid gland.[43] It is clear, therefore, that the basal heat production may be altered by at least three factors—the thyroid, the adrenal cortex and the involuntary nervous system.

Summary and Conclusions. 1. A study made at a seaport of 55 individuals with thyroid enlargement is presented.

2. None of these patients presented sympathomimetic manifestations or alterations of their basal metabolism.

3. The efficacy of iodides in reducing neck circumference is again demonstrated.

4. The thyroid enlargement where uniform is due to existing hyperplasia or the results of a previous hyperplasia.

5. The mechanism of the production of hyperplasia is through diminution in the iodine store.

6. We are unaware of the mechanism that produces the deficiency in the iodine store.

7. Alterations in the iodine store throw no light on the function of the gland.

8. Hyperplasia of the thyroid gland is compatible with normal economy, and it may be present in cretinism.

9. That hyperplasia of the thyroid gland indicates hypersecretion is based on inferences which are not compatible with the available data.

10. Discrete enlargements of the thyroid gland are due to cysts or adenomata. Cysts are of no functional importance. Adenomata function apparently in no way different from non-tumor tissue, except that they are less active in their avidity and response to iodine.

11. There is no evidence to support the theory of the toxicity of adenomata.

12. The influence of nervous impulses upon the secretion of the thyroid gland has not been demonstrated, and in view of the subtle chemical reaction the nervous influences probably play a minor role, if any.

13. While the active principle of the thyroid gland has been isolated, we are as yet unable to make any determinations upon the rate of secretion.

14. Feeding thyroid extract in toxic amounts does not reproduce Graves' syndrome.

15. The role of the thyroid in the production of clinical symptoms is greatly overemphasized. Of the 55 patients recorded, in 41 attention had been specifically directed to the thyroid gland. Either the symptoms were attributed to a disturbance of the function of the gland, while the true pathological condition that was operative was overlooked, or else specific therapy was directed toward the thyroid gland without any relief of symptoms which could not possibly have been caused by thyroid disturbance.

16. Roentgen-ray exposures of the thyroid gland do not cause an appreciable reduction in size.

17. Operations upon the thyroid gland may be followed by compensatory hyperplasia.

18. Thyroid enlargement can be present for many years without in any way altering the bodily economy.

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ON THE SIGNIFICANCE OF THE SEQUENCE AND MODE OF DEVELOPMENT OF SYMPTOMS AS AN AID TO THE DIAGNOSIS OF MULTIPLE SCLEROSIS IN THE EARLY STAGES.*

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Multiple sclerosis is regarded by European authors as one of the most frequent conditions that affect the central nervous system. The number of cases of multiple sclerosis, however, in which the clinical diagnosis can be made with certainty by no means exceeds the number of cases in which the differential diagnosis is perplexing. Spiller, as well as Taylor, has drawn attention to the infrequency with which cases of multiple sclerosis with necropsy are recorded in this country, an apparent rarity that is probably due to the great difficulty with which the clinical diagnosis is made.

Considerable difference of opinion seems to exist regarding the symptom-complex that would justify a diagnosis of multiple sclerosis, particularly during the early stages of the disease. When Charcot, in his earlier descriptions, emphasized the importance of such symptoms as intention tremor, nystagmus, and scanning speech, he did not wish to imply that these manifestations were an invariable accompaniment of the disease, and most neurologists now agree that a positive diagnosis of multiple sclerosis may be

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justifiable even in those cases in which the three classic signs of Charcot are not present at the same time. Great stress must, however, be laid upon all the points in the history, to show the sequence in the development of subjective and objective signs arising during the course in a given case. This view is of great importance in diagnosis, since it brings about a broader conception of the disease and tends to create a unanimity of opinion, as well as to help toward an appreciation of the mildest types of the disease that might lead to the realization that abortive cases or spontaneous cures do occur. Thus far this theory has not been confirmed.

For purposes of logical discussion it is necessary to state briefly that the clinical and histologic evidences that have been recorded up to date[1] seem to us to be strongly in favor of the view that the disease possesses a distinct entity, and that it is essentially infectious in origin and inflammatory in character, notwithstanding the fact that there is considerable evidence to show that the symptoms of multiple sclerosis may be produced by other diseases. Thus, for example, Spiller and Camp[2] reported a case of malarial fever that presented symptoms similar to those of multiple sclerosis. These authors[3] also found a form of multiple sclerosis that was syphilitic in origin. Other investigators have made similar observations. In another case reported by Mills and Spiller[4] the symptoms were found to be due to arteriosclerosis. We are convinced that in one of our cases (Case I) the disease was directly related to a previous attack of "influenza" and epidemic encephalitis. The relation of multiple sclerosis, both clinically and histologically, to epidemic (lethargic) encephalitis is a subject of great importance, and merits careful individual consideration.

During this meeting Dr. Spiller will demonstrate the microscopic lesions of the central nervous system in cases of epidemic encephalitis which very closely resemble those observed in certain cases of multiple sclerosis.[5] Years ago, Marie, Oppenheim, and others commented upon the relation of influenza to multiple sclerosis. The relation of influenza to epidemic encephalitis, although not proved, is admitted by many. These unsettled problems are referred to here more particularly to emphasize the fact that the knowledge that an infectious process had existed before the earliest symptoms of multiple sclerosis developed may be of importance in forming the diagnosis.

In the earliest stages of multiple sclerosis many of the symptoms

[1] Dawson: Review of Neurology and Psychiatry, 1917, **15**, 47; 1918, **16**, 287.
[2] Am. Jour. Med. Sci., 1900, **120**, 629.
[3] Spiller and Camp: Jour. Nerv. and Ment. Dis., 1907, **34**, 760.
[4] Jour. Nerv. and Ment. Dis., 1909, **36**, 747.
[5] Since the preparation of this manuscript, Dr. Spiller presented before the Philadelphia Neurological Society, at the meeting of February 27, 1922, a report on a form of epidemic encephalitis that resembled, both clinically and histologically, multiple sclerosis.

are so mild as to escape detection. It must be remembered, however, that these symptoms may subside without leaving any trace, and yet recur later and become progressively more intense. The most minute cross-examination on the part of the physician is, therefore, necessary in order to determine the mode of succession of the objective signs in a given case; this requires so much time and patience that it is not at all surprising that but little can be gained for this particular purpose from a study of many of the histories that are recorded in routine hospital practice.

If, in a given case, spastic paraplegia, intention tremor, scanning speech, optic atrophy, and nystagmus are present, the diagnosis presents but little difficulty, since these symptoms point to an advanced stage of the disease. But in the earliest stages of multiple sclerosis, before any of these signs have developed fully, the diagnosis is exceedingly difficult. The point that we wish to emphasize and discuss at this time is that a knowledge of the mode of succession of the symptoms may constitute sufficient evidence on which to base a positive diagnosis in the early and undeveloped stages. When accurate information is obtainable, a careful analysis of all the circumstances leading up to the development of the very earliest forms of disability is of as much value for diagnostic purposes as are the individual symptoms. Isolated objective signs, such as impairment of vision, ocular paralyses, weakness of one or more of the extremities, associated with paresthesia, are exceedingly common. These phenomena are, however, transitory, and are frequently so fleeting as to be overlooked.

Remission of the onset symptoms is far more common than is generally believed, and is prone to occur in the majority of cases. Birley and Dudgeon[6] have shown that most cases run an intermittent course, accompanied by a haphazard series of relatively acute disturbances due to focal lesions.

In one of the cases (II) studied at the University Hospital the earliest evidence of the disease, dating back to 1907, was a paralysis of the left leg that lasted one month, disappeared, and returned within two months. It was absent again for a prolonged period, but in 1909 it recurred, and remained as an intermittent feature up to and for some time after the full development of marked bilateral spastic paraplegia and other symptoms of multiple sclerosis about eight years later.

This case shows that transitory paralyses may constitute the only objective sign of disease, and may recur and subside at irregular intervals, covering a period of time varying in duration from months to years, and gradually becoming fixed and permanent, and later associated with other manifestations characteristic of the late stages of multiple sclerosis.

[6] Brain, London, 1921, **44**, 150.

In one of our cases (III) the only complaint was of intermittent diplopia over a period of three years before other characteristic signs developed. In another case (IV) there were irregular attacks of sudden but transient blindness preceding the development of optic atrophy; and in still another case (V) there developed very rapidly bilateral oculomotor paralysis that persisted for eighteen months, no other symptoms, either objective or subjective, being present. Tremor, scanning speech, and weakness of the extremities developed later. Case VI presented the signs typical of hemiplegia of rapid onset, which had been mistaken for the results of an apoplectic attack from vascular occlusion; these persisted for a number of months without the development of other symptoms. Numerous similar examples could easily be collected, since they appear to be quite common, and tend to show the difficulties in diagnosis in the earliest stage in the absence of other phenomena.

For diagnostic purposes isolated symptoms of the disease under consideration are of little value, but the knowledge that paralytic phenomena were at first isolated and later became permanent and were combined with nystagmus, scanning speech, tremor, or other manifestations may be of considerable importance.

It has been our experience that the classic symptoms, *i. e.*, nystagmus, scanning speech, and intention tremor, differ from the other signs of this disease in that they are not so frequently remittent in character, although occasionally they appear as isolated signs. Once established, they tend to become permanent and to progress. Each of these symptoms seems to point to a more or less widespread distribution of the inflammatory lesions, and for this reason they are of far greater importance than almost any other single sign of the disease. Scanning speech or other dysarthria indicates disturbance in the combined motor function of the respiratory, laryngeal, palatal, lingual, and lip muscles that are supplied by different cranial nerves; and each one of these cranial nerves has its origin at a different level within the brain-stem. One lesion sufficiently severe to have destroyed all of these must, therefore, be very diffuse.

A purely spinal type of multiple sclerosis is exceedingly uncommon. It is not unusual, however, to find that a diagnosis of multiple sclerosis has been made when the symptoms of spastic paraplegia and loss of abdominal reflexes are present without any involvement of the structure of the brain. In our opinion this is not always justified, although we do not deny that the disease may present this picture. A case of this kind was reported in 1900 by Burr and McCarthy,[7] the diagnosis having been confirmed by autopsy, but which presented only the signs of combined sclerosis of the spinal cord. When, however, these symptoms are followed by

[7] Jour. Nerv. and Ment. Dis., 1900, **207**, 634.

nystagmus, intention tremor, or scanning speech, the diagnosis is, we believe, clear. Such a case recently came to our notice, in which spastic paraplegia had existed for two years, after which nystagmus, scanning speech, and tremor of the upper limbs rapidly developed. Other cases have been reported in which symptoms attributable to the spinal cord were entirely lacking. Here, again, in the absence of the classic trio, scanning speech, nystagmus, and intention tremor, the diagnosis may be uncertain. Thus in Case V bilateral oculomotor paralysis developed very rapidly in the spring of 1919, and persisted for eighteen months, although no cause for it could be found. Months later, however, the patient began to complain of difficulty in writing with his right hand, due to tremulousness. This tremor gradually extended, until now it involves the four extremities and is associated with moderate weakness in the right lower limb, increased tendon reflexes, and the Babinski sign, ankle clonus, and scanning speech. At the beginning a diagnosis of multiple sclerosis was impossible, but now that the other symptoms have developed, together with the involvement of the lower limbs, the diagnosis seems quite clear.

Conclusion. We would emphasize that the sequence, mode of development, and the combination of signs are more important than the individual symptoms themselves. In addition, the occurrence of cerebral symptoms, most particularly scanning speech and nystagmus, either alone or after spinal symptoms have developed, or the reverse, spinal symptoms following the cerebral manifestations, is strongly indicative of the dissemination of the pathologic process. If there is a history of earlier remissions or of a discontinuance of the process in the early stages, followed by a progressive course, the nature of the disease can be determined with considerable accuracy. With the exception of syphilis, no subacute or chronic disease other than multiple sclerosis presents this remittent picture so constantly.

Case Reports. CASE I.—J. K., aged eighteen years.

Chief Complaint. Tremulousness.

Family History. Negative.

Personal History. Was well until October, 1918, when he was very ill with "flu." Was confined to bed for two weeks; fever and delirium were present and patient was extremely weak. He gradually recovered from his acute symptoms, and was out of bed in about four weeks. Although believed to have fully recovered, he states that he has never regained his strength, particularly in his lower limbs. About January, 1919, while driving a motor car at night and looking at the headlights of another car approaching, he first noticed diplopia. This has been irregular and inconstant, but most annoying. During this time he has developed very gradually weakness of the lower limbs, associated with marked

tremor and uncertainty in gait. General health remained fairly good.

Examination showed weakness of the right sixth and of the left third nerve; marked intention tremor of all four limbs; adiadokokinesia on each side; dysmetria in both upper limbs; marked ataxia and spasticity of both lower extremities; increase of all the tendon reflexes; ankle clonus on the right and Babinski sign present; speech is slurring.

Diagnosis. Multiple sclerosis developing after an attack of "flu."

CASE II.—E. Z. D. White male, aged thirty-three years. First examined April 20, 1911.

Chief Complaint. Weakness of the left leg.

Family History. Negative.

Personal History. The patient is a highly educated man. He has been partially blind since 1908, the impairment being due to unilateral optic atrophy, considered by the ophthalmologist to be the result of a sphenoidal sinusitis. There was some difficulty in convergence at this time, believed to have been due to weakness of the internal rectus muscle of the left eye. About a year preceding the difficulty with his eye (1907) he noticed a weakness of the left leg which lasted about one month, disappeared for two months, then recurred for about a month, disappeared again, and recurred in 1909. Shortly after the last recurrence he experienced difficulty in writing and in shaving, which he attributed to weakness and stiffness of the right hand and arm.

Following the appearance of these symptoms he gradually developed a spastic paraplegia, scanning speech, and intention tremor—a typical picture of *disseminated sclerosis*, from which condition he is suffering at the present time.

Blood Wassermann was negative.

CASE III.—K. N., white female, aged eighteen years. First examined in 1905.

Chief Complaint. Nervousness.

Personal History. For about a year she has had attacks of double vision lasting for varying periods of time, the longest being seven weeks. After several attacks of double vision during a period of three years she gradually developed a marked tremulousness of the hands and noticed disturbances of speech. Following this her symptoms progressed quite rapidly, and she died two years after first coming under observation. This was a typical advanced case of *disseminated sclerosis.*

CASE IV.—W. W. P. White male, aged twenty-four years. First examined February 2, 1916.

Chief Complaint. Nervousness.

Personal History. The patient states that he was perfectly well up to December, 1915, at which time he suffered a severe nervous shock, and immediately after noticed that his vision was blurred. Within a few days be became blind and had some trembling of the hands and a slight difficulty in walking. All these symptoms disappeared completely. About two weeks previous to his admission to the hospital he again developed tremulousness of the hands, and had considerable difficulty in using his legs for locomotion. He gave no history of excesses of any kind, and was a man of unusual education and of splendid physique.

Physical examination at the time of his admission to the hospital presented the neurologic features of a fairly well-advanced case of *disseminated sclerosis*, namely, intention tremor, scanning speech, spastic paraplegia, and optic atrophy.

He remained in the hospital for a short time, and was under observation for about two years. Within six months after leaving the hospital he improved so greatly that he was regarded as almost completely recovered. This remission in the symptomatology was of very short duration, however, and the symptoms that followed progressed with tremendous rapidity. At this time he presents a picture of a well-marked case of *disseminated sclerosis*, and is almost helpless.

Wassermann reaction, both of the blood and of the spinal fluid, was negative.

CASE V.—J. W., aged seventeen years.

Chief Complaint. Headache and inability to look upward.

Personal History. In May, 1919, following an acute attack that was diagnosed as "flu," and that had confined him to bed for two weeks, the patient found that he was unable to look upward or downward, and had frequent severe frontal headaches. On examination in June, 1919, there was inability to rotate either eyeball upward or downward, although the external and internal rotations were performed normally. No cause for the condition could be determined, and no other objective sign could be discovered. The patient continued under observation at the Presbyterian Hospital, and about October, 1919, he complained of an inability to write because of tremor of the right hand. This condition progressed, and weakness of the right lower limb also developed. About 1920 his speech became indistinct, and in 1921 examination showed partial bilateral third nerve paralysis, with marked scanning speech, intention tremor, dysmetria, and adiadokokinesia on both sides, but most marked on the right, weakness of the right lower limb, with ankle clonus and increased tendon reflexes.

Diagnosis. Multiple sclerosis.

CASE VI.—M. S. White male. First examined at the Philadelphia General Hospital.

Personal History. Patient was almost completely blind. The right half of his body was practically powerless, and he had considerable difficulty in using the left side of his body. Nevertheless, he was able to move about. The history of his present illness was to the effect that about a year before coming to the hospital he had a sudden attack of what was believed to have been "an apoplectic stroke, which resulted in paralysis of the right arm and right leg." This was soon followed by failure of vision, which gradually grew worse.

On admission to the hospital he presented weakness of all four limbs, but greater on the right side; a partial blindness, due to optic atrophy; slurring speech; marked nystagmus; tremor of the left upper extremity following use of the limb; marked increase of all the reflexes, and bilateral Babinski sign.

Wassermann, both of the blood and of the spinal fluid, was negative, as was also the general physical examination.

The disease pursued a continued progressive and typical course up to the time of death, which occurred in 1921.

Diagnosis. Disseminated sclerosis.

OBSERVATIONS REGARDING THE CONDITION OF TRAUMATIC CEREBRAL EDEMA.

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WITHIN recent years the presence or not of a linear fracture of the vault or of the base of the skull in conditions of brain injury has become of comparative unimportance, whereas the degree of associated cerebral edema has become more and more a significant factor to be considered in the diagnosis and in the treatment of these patients, not only during the acute condition but for a period of months and even of years following the cranial injury. Varying degrees of cerebral edema undoubtedly accompany all severe cranial injuries, whether there is a fracture of the skull or not and whether there is an associated intracranial hemorrhage or not, and it is difficult to conceive that a traumatic intracranial hemorrhage can occur without there being associated with it a cerebral edema of more or less severity and especially of the localized type.

By the term cerebral edema is understood a "wet" edematous condition of the cerebral tissues. Most probably it is merely an

excess amount of normal cerebrospinal fluid; in this regard the condition of cerebral edema differs from the edema of other body tissues following a bruise or injury and it is, therefore, not simply a transudation of lymph. The excess amount of cerebrospinal fluid in the acute traumatic cerebral conditions may be due to hypersecretion of the fluid from the blood stream on the part of the choroid plexus in the third ventricle, or, and most probably, in my opinion, it is due to a lessened absorption (hypoexcretion) of the cerebrospinal fluid through the normal excretory channels, chiefly in the walls of the supracortical veins, sinuses and Pacchionian bodies, and thus a partial blockage of the excretion of the cerebrospinal fluid is temporarily produced. It is not known whether or not this lessened excretion of the cerebrospinal fluid through the little stomata of exit in the walls of the supracortical veins and sinuses in these acute traumatic conditions, is due to the associated vasomotor disturbance—in effect, a paralytic retardation of the excretory function of the supracortical veins. It is an interesting observation, however, that, during the period of severe initial shock so frequently following the cranial injury, the condition of cerebral edema is rarely present; this may be due to the associated lowered blood-pressure, both general and intracranial, and, therefore, resulting in possibly a diminished secretion of the cerebrospinal fluid by the choroid plexus, so that the condition of cerebral edema does not occur during this period of shock, even though at the same time the excretory function is also lessened as a result of the condition of shock and its accompanying vasomotor disturbances.

Cerebral edema of toxic origin, such as occurs in nephritic and diabetic disease and in alcoholic and arteriosclerotic patients, is most probably due to an increased secretion of the cerebrospinal fluid rather than to a partial blockage of its excretion through the little stomata of exit in the walls of the supracortical veins lying in the sulci between the convolutions of the cerebral cortex—the chief channels of the normal excretion of the cerebrospinal fluid, and, to a lesser degree, through the walls of the Pacchionian bodies and of the large dural sinuses into the blood stream. Cerebral edema, resulting from toxic conditions, is, therefore, most probably due to a hypersecretion rather than to a lessened absorption or partial blockage of the excretion of the cerebrospinal fluid, and yet in acute traumatic cranial conditions associated with cerebral edema of varying degree, it is not definitely known whether the "wet" edematous brain of an excess amount of cerebrospinal fluid is due to a temporary increase of the secretion or, and more probably, to a decrease in the amount of absorption or excretion of the cerebrospinal fluid.

In reviewing the literature upon cerebral edema of traumatic origin, it has indeed been most surprising to realize the apparently

slight interest in this serious complication of cranial injuries; the literature itself is most meagre and with the exception of papers by Jones,[1] Baehr,[2] Preston,[3] Hollander,[4] Reichardt[5] and two or three others, and brief mention of the condition in various general surgical treatises and text-books, such as Rawling, Keen, Mills, Stewart and Herrick, little or no attention has been directed toward a better clinical understanding of the condition and its treatment. It is only within recent years that the factor of cerebral edema in conditions of brain injuries has been recognized as being a most important one, not only from the standpoint of the diagnosis, but of the treatment and of the prognosis. Traumatic localized cerebral edema, however, has frequently been diagnosed as a possibility in producing various neurologic signs, such as the alteration of the reflexes, paralyses of varying degree and occasionally aphasia in its various forms, and the diagnosis itself has been confirmed, in selected cases at operation, immediately upon opening the dura and thus permitting a careful exposure of the involved cerebral cortex.[6]

In those cases of localized cerebral edema developing from the associated operative traumatism of opening the bone and the dura, and of the effect of cold air upon the cortex, producing a dilatation of the supracortical veins and thus a temporary partial blockage of the excretion of the cerebrospinal fluid, a localized cerebral edema can develop within a few minutes to the extent that the involved cerebral cortex may bulge and tend to protrude through the dural opening; a lumbar puncture with spinal drainage, however, will usually permit the protrusion to recede so that no cortical damage results.

Until several years ago, patients dying within twelve to forty-eight hours following a cranial injury, were usually diagnosed as conditions of "shock," "fracture of the skull," "hemorrhage of the brain," and yet when an autopsy was performed (and only too frequently the importance of autopsy findings has been overlooked)[7]

[1] Jour. Am. Med. Assn., 1918, **11**, 1265.
[2] Lancet-Clinic, 1914, **111**, 696.
[3] Jour. Nerv. and Ment. Dis., 1894, **21**, 494.
[4] Jahrb. f. Psychiat., Wien, 1882, **3**, 176.
[5] Allg. Ztschr. f. Psychiat., Berlin, 1918, **12**, 622.
[6] Vide report of case of localized cerebral edema by my associate, Dr. G. E. Espejo, Jour. Am. Med. Assn., 1918, **70**, 1278.
[7] During the past seven years I have insisted, before performing an operation upon any patient having a chronic neurologic condition, that the nearest relatives give me, in writing, permission to make a postmortem examination in case the patient should die (and naturally one does not expect the patient to die), in order to ascertain the real cause of death rather than accept the common report of "shock," "cerebral or pulmonary embolus" and "thrombus formation." If death is due to an operative error or to some avoidable complication, then it is for the surgeon to realize it so that its repetition can, if possible, be prevented in future patients; moreover, the accuracy of the diagnosis is thus confirmed or disproved and the pathologic lesion is carefully examined. The coöperation of the nearest relative in permitting these examinations has been the rule; in only two instances in a series of over 1000 patients operated upon was a flat refusal maintained, and no operation was performed.

the report was often characterized as being "merely a wet brain," thus apparently confirming the diagnosis of "shock," but not always that of "fracture of the skull" or of "cerebral hemorrhage." If, however, a fracture of the vault and particularly of the base of the skull was disclosed, and, especially, if an area of subdural hemorrhage could be demonstrated, then the diagnosis was considered complete—the cause of death ascertained. This was, and is, so often the case in the large municipal hospitals, where many nephritic and arteriosclerotic patients associated with the condition of chronic alcoholism are admitted following cranial injuries of even an apparently trivial nature and yet, upon autopsy within several days, merely a wet edematous condition of the brain is disclosed; shock is a definite factor in the high mortality in many of these patients, but the condition of acute cerebral edema producing a marked increase in the intracranial pressure is a far more serious and important complication in the diagnosis and treatment of these patients. The presence or absence of a fracture of the skull, either of the vault or of the base, and the presence or absence of a small amount of intracranial hemorrhage, even though the cerebrospinal fluid may be termed bloody at lumbar puncture, is of little significance in the treatment and prognosis of the condition. The most important point to be considered is the presence or not of a marked increase of the pressure of the cerebrospinal fluid, whether due to hemorrhage or to cerebral edema or to both; it is this factor of increased intracranial pressure which has been overlooked so frequently in the past, unless it was of such a height as to produce the definite and, unfortunately, the late signs of medullary compression—increased blood-pressure, retarded pulse and respiration-rates with the irregular Cheyne-Stokes rhythm—a most serious condition for the patient, as the chances of recovery of even life, not to mention normality, are not favorable.

No doubt the condition of severe initial shock is a frequent cause of death in cranial injuries, and in these extreme cases the diagnosis can usually be made from the clinical charts alone: subnormal temperature, pulse- and respiration-rates increased to 140 plus and 40 plus, respectively, and the blood-pressure 90 and lower, and yet this diagnosis of shock as being the cause of death has been frequently asserted in the presence of a temperature of 100 plus, pulse and respiration rates of 70 and 16 and lower, respectively, and a blood-pressure of 140 plus. At autopsy upon a number of these patients, who finally succumbed from the more advanced signs of medullary compression and, finally, of medullary edema—rapidly rising temperature to 106 plus, pulse and respiration rates of 160 plus and 50 plus, respectively, and a falling blood-pressure of 80 and lower, only too frequently in these cases was "merely" a cerebral edema ascertained and no fracture or even intracranial hemorrhage disclosed; the condition of shock might

have been an initial factor in precipitating the acute medullary edema, but surely the cause of death and the diagnosis should not be labelled as one of "shock." In a recent work upon the diagnosis and treatment of brain injuries,[8] I realize now that I did not emphasize sufficiently the relative unimportance, in my opinion, of a definite increase of the blood-pressure, except as indicating the lateness of the time for operative interference, since this increase of the blood-pressure is a sign of medullary compression, and the patient should be given an opportunity to recover by an earlier lowering of the increased intracranial pressure, either by the expectant palliative or by the operative method. If we wait in the treatment until the blood-pressure is definitely increased above normal, then we are letting the patient reach a very serious condition of medullary compression and it is then frequently too late to aid him even with an operation of decompression and drainage. In my opinion, the ophthalmoscopic and spinal mercurial manometric findings are much more valuable than the status of the blood-pressure, as definite and delicate tests in ascertaining *early* the intracranial condition of an increase of the intracranial pressure, whether due to hemorrhage or to an excess cerebrospinal fluid. The presence of shock is characterized by a lowered blood-pressure together with a subnormal temperature and an increased pulse-rate, whereas the stage of medullary edema presents a rising temperature, pulse- and respiration-rates, and also a falling blood-pressure, so that clinically these two periods can usually be differentiated. It is the general neglect in the recognition of the importance of the factor of cerebral edema in the diagnosis and treatment of brain injuries that will be discussed in this paper.

The significance of cerebral edema as being the most important factor in the statistics of the high mortality following cranial injuries in patients of the large municipal hospitals, is just being recognized, and their high mortality-rate cannot be compared, with justice, to the much lower rate in private patients or in the patients of the smaller private hospitals; this natural difference is due to the lessened general resistance of the majority of patients admitted to the municipal hospitals with severe cerebral injuries, a lessened resistance to the onset of acute cerebral edema following even apparently trivial cranial injuries and due to chronic alcoholism associated with varying degrees of nephritis and arteriosclerosis. These patients are poor risks and their prognosis is always much more grave than in patients of good habits and especially in the absence of nephritis and arteriosclerosis, because in the latter selected patients a dangerous degree of cerebral edema is only to be feared as the result of *severe* cerebral injuries and not

[8] The Diagnosis and Treatment of Brain Injuries, with and without a Fracture of the Skull, J. B. Lippincott Company, Philadelphia, 1921.

following the milder type of cranial injuries. This is true also of children, in whom traumatic cerebral edema is a rare complication unless the cerebral injury is of the greatest severity. Therefore, the mortality-rate of brain injuries in children and adolescents is much lower than in adults of either sex; and in a rather large series of acute brain injuries, the mortality-rate in the female patients has been definitely lower than that of the male patients, most probably due to the greater resistance of women to the onset and development of cerebral edema, owing to their better habits of life in regard to alcohol and to the strain and stress of modern life, and thus a greater freedom from arteriosclerotic disease. In this connection, it may be of interest to note that the increased intracranial pressure developing in children of either sex and in adult female patients, following cranial injuries with or without a fracture of the skull, less frequently reaches a height necessitating the operative treatment of decompression and drainage than in adult male patients, because in the former patients (women and children) the condition of extensive cerebral edema is only associated with the severe types of cerebral injuries, and, therefore, the expectant palliative treatment of absolute rest, quiet, ice helmet, liquid diet and catharsis usually suffices to obtain an excellent recovery of life and of normal function; while in the adult male patients, the greater frequency of the development of extensive cerebral edema necessitates in a larger proportion of these patients the operation of subtemporal decompression and drainage in order to obtain the best results by an early lowering of the resulting increased intracranial pressure.

Acute Cerebral Edema. The onset of acute cerebral edema with and without an intracranial hemorrhage may occur so rapidly following the cranial injury that the initial period of shock is obscured and overshadowed by the signs of high intracranial pressure, due to the excess amount of cerebrospinal fluid associated or not with varying degrees of hemorrhage. In these severe cases the signs of medullary edema resulting from the extreme condition of cerebral edema may be evident upon the patient's admission to the hospital—rapidly rising temperature of 104° plus, pulse and respiration rates increasing to 140 plus and 40 plus, respectively, while the blood-pressure falls steadily; naturally in these extreme cases the condition is a hopeless one, the patients being moribund. They all die, operation or no operation. In this regard it may be stated that no patient should be operated upon during the terminal period of medullary edema, cerebral surgery being thereby merely discredited, and this moribund period together with that of the initial stage of extreme shock immediately following the injury form the two periods of brain injuries when no operation should be performed, and if a patient should recover following an operation during the period of severe initial shock,

then he recovers in spite of the operation. It has been the neglect in observing and in recognizing in the past the danger as well as the futility of operating during these two periods that has discouraged the operative treatment of brain injuries during *any* period, and thus the rational treatment of these acute patients has lagged behind the great advances of modern surgery.

In a much larger percentage of the patients developing an extensive cerebral edema, the onset of the condition is by no means such a rapid and overwhelming one; the condition of the patient upon admission to the hospital and even for several days may be considered as "fair" or indeed "good;" a normal temperature or a slightly elevated one, pulse and respiration rates normal or mildly increased respectively, and a blood-pressure within physiologic limits; then gradually the pulse and respiration rates descend slowly during a period of hours to 70 and 18 and then to 60 and 16, respectively, and even lower, and the blood-pressure possibly (but by no means always) rises to 140 and occasionally higher, and yet the temperature remains the same. It is during this period of mild medullary compression that it is most important to ascertain the presence or not of a high intracranial pressure, as indicated in the fundi ophthalmoscopically and by means of the spinal mercurial manometer at lumbar puncture.[9] If the mercurial manometer should register the pressure of the cerebrospinal fluid less than twice the normal pressure, which is 6 to 8 mm., then, whether the cerebrospinal fluid is bloody or not, the expectant palliative treatment, with or without the repeated lumbar punctures of spinal drainage, will usually suffice to obtain excellent recovery of both life and apparent normality in slightly over two-thirds of the patients, whereas if the pressure of the cerebrospinal fluid at lumbar puncture is greater than twice the normal pressure (that is, over 16 mm.), then in my opinion, these selected patients should receive the benefits of an early subtemporal decompression and drainage—both to assure a recovery of life and, more especially, to permit the greatest return of normal

[9] The condition of measurable papilledema to the degree of "choked disks" (2 D+) is rarely to be observed with the ophthalmoscope in those patients having acute brain injuries; a measurable papilledema does occur when the intracranial pressure is extreme and of slow formation, as in cases of large middle meningeal extradural hemorrhage and thus producing a tumor pressure, but the usual fundal picture in the acute patients having a definite increase of the intracranial pressure is that of dilated retinal veins associated with an edematous blurring of the nasal and temporal margins and of the nasal halves of the optic disks. During the period of initial shock following the cranial injury, it is most uncommon for ophthalmoscopic examinations to disclose the fundal signs of an increased intracranial pressure—the general blood-pressure being lowered and, therefore, it is physiologically impossible for a high intracranial pressure to develop even if a large vessel or sinus is torn; in this manner, the condition of initial shock within moderate limits may be a most valuable aid of Nature in affording the organism a period of time to readjust itself to changed intracranial conditions—by the thrombosis of torn vessels and thus avoiding or at least lessening the later intracranial hemorrhage.

function physically, mentally and emotionally. These patients with high intracranial pressure, even to the degree of medullary compression, may recover with life without an operation, and a large number of the milder ones do, but the percentage of recovery of normal function, let alone life itself, is very low indeed in this class of patients and when recovery of life does occur, then it is most rare to obtain as normal an individual as before the injury. These are the patients forming a large class of chronic brain injuries and their condition will be discussed under the heading of chronic cerebral edema. The technic of cerebral surgery has so advanced during the past two decades, and especially the operation of subtemporal decompression as devised by Cushing, that these operations should no longer be deferred until the patient reaches the most serious stage of extreme medullary compression, but rather an early operative lowering of the high intracranial pressure will permit not only a higher percentage of recovery of life, but in some cases of even greater importance, the maximum degree of normality. In this series of over 1000 patients, upon whom the subtemporal decompression was performed, the mortality was only slightly over 10 per cent.

In adults, and especially in alcoholic males, the onset of acute cerebral edema following even apparently trivial injuries of the head may develop so rapidly and to such a degree that upon admission to the hospital the condition has become one of medullary edema—rising temperature, pulse and respiration rates with a falling blood-pressure; the period of initial shock in these patients may be of very short duration and at times it would seem that the condition of shock merges directly into that of medullary edema without there having been evident the clinical signs of medullary compression—moderate temperature, lowered pulse and respiration rates and a possible increase of the blood-pressure. The condition in these extreme cases may have been so overwhelming that the signs of medullary compression were only obscured rather than being absent. At autopsy, however, the usual findings are a very "wet" edematous brain under high tension, associated or not with hemorrhage of varying degree with or without a fracture of the skull. These acute and extreme cases occur only too frequently in active hospital practice, and they are the moribund patients for whom little if anything can be done; and most assuredly, *no* operation. On the other hand, those patients eventually developing the condition of acute cerebral edema after a period of twelve to forty-eight hours, and especially after several days to even two weeks following the injury, they are the ones whose clinical charts are typical—the usual period of initial shock of varying degree and of several hours' duration, then the general condition of the patient so improves that an excellent prognosis may be stated; with the exception of headache, the patient may have no com-

plaints. After a period of hours or even days, the pulse rate may descend slightly to 74 and to 70 and the respirations register 20 and later 18, yet "the temperature is slightly increased and the blood-pressure is normal," and the excellent prognosis is reassured with the expectant palliative treatment. The condition seems favorable and fortunately in many patients the recovery is uneventful; on the contrary, however, the pulse- and respiration-rates may continue to descend to 62 and to 16 respectively, and may even remain in this relative position for a period of hours and of several days, and the temperature only slightly increased and the blood-pressure possibly raised a few points; "still the patient is perfectly conscious, a little drowsy and the headache is only natural." Even from this condition of evident mild medullary compression, the patient may recover with life after a period of days and weeks and with the expectant palliative treatment alone, but it is this type of patient who so frequently never regains his former normality, especially in the mental processes and the emotional reactions. But should this condition of mild medullary compression remain apparently stationary for a period of days and should then, either suddenly (within two to six hours) or gradually (twelve to forty-eight hours), progress to the degree that the pulse- and respiration-rates descend to 54 and 16, and lower, respectively, then this mild condition of medullary compression becomes the most serious one of severe medullary compression, which may rapidly change into that of medullary edema in spite of any known treatment, operative or otherwise; and once the temperature rises rapidly to a 104 plus, the pulse rate to 70, 80, 100, 120, 140 plus and the respiration rate to 18, 22, 28, 34, 40 plus and the blood-pressure to fall steadily—the typical onset of medullary edema—then all treatment is futile and these patients all die within twelve to forty-eight hours. To permit patients to reach this degree of extreme intracranial pressure during a period of hours and even of days, and sufficient to produce the signs of medullary compression, without ascertaining accurately and frequently the intracranial pressure, by means of routine examination of the fundi with the ophthalmoscope, and especially by the repeated daily use of the spinal mercurial manometer, medical treatment of this careless character is typical of the period of at least twenty years ago, when it was considered remarkable for a patient to recover with life "and a fracture of the base of the skull was present." The rational treatment of brain injuries depends chiefly upon the presence or not of a marked increase of the intracranial pressure, whether due to hemorrhage or to cerebral edema or to both, and the clinical signs of medullary compression should not be awaited before the patient is given an opportunity to recover not only life but the former normality. If an operation is advised, then the operation of choice is the subtemporal decompression and

drainage, removing an area of bone two to three inches in diameter beneath the temporal muscle and opening the dura widely and permitting it to remain open. These apparent elementals in the operative treatment of brain injuries are mentioned because only recently, in the year 1921 in New York City at a large active hospital, the leading surgeon operated "to relieve a brain pressure following a fracture of the skull with hemorrhage" by turning down a large bone flap over the motor area with a hammer and chisel and then pricked the dura to permit the underlying hemorrhage to escape (several drops); the bone flap was then replaced and the relief of intradural pressure was practically *nil;* this procedure may be called an operation, but by no means a useful one.

It has long been recognized that children and young adults withstand the effects of cranial injuries much better than patients over forty years of age, and unless there are present in these young patients definite contusions and lacerations of cerebral tissues, then the associated cerebral edema is only of moderate degree; as gross lesions of the cerebral tissues in these traumatic cases of peacetimes are unusual (only occurring in 12 per cent of the acute cases in this series of 582 patients), their much lower mortality-rate is explained by the comparative absence of the extreme condition of cerebral edema and thus a relatively lower intracranial pressure, usually insufficient to produce the signs of medullary compression and the subsequent medullary edema. It is for this reason—the comparative rarity of extensive traumatic cerebral edema in children and young adults—that makes possible in the large majority of cases their successful treatment with the expectant palliative method alone, whereas in the older patients the greater frequency of the development of an extreme degree of cerebral edema with the resulting high intracranial pressure necessitates in a large percentage the operative method of treatment; however, even in the adult cases of this series the operative treatment was considered advisable in only 31 per cent, the expectant palliative method being sufficient in slightly over two-thirds of the patients.

In this connection, I should like to report briefly the case history of a child developing an extreme condition of acute cerebral edema several days following the cranial injury; unless the cerebral tissues are badly contused or lacerated, not only is it uncommon for a child to develop such a marked condition of acute traumatic cerebral edema as to make obligatory a cranial decompression and drainage, but that the onset of the resulting high intracranial pressure should be delayed until four and a half days after the cranial injury and the edematous condition should then persist in a mild degree (in spite of the drainage operation) for a period of several weeks—these are the unusual features of this case history.

No. 1741. Edward, aged seven years; white; school; United States. Admitted, October 9, 1921, to the Swiney Sanitarium, Bayonne, N. J. Operation, October 14, 1921 (3 A.M.), four and a half days after the injury. Left subtemporal decompression and drainage. Discharged, November 23, 1921, forty-three days after injury. Family and past medical histories were negative. Usual diseases of childhood.

Present Illness. While playing at home, the patient fell headlong down the stairway, striking upon the top and left side of head; stunned but no complete loss of consciousness. No bleeding from nose or ears. Immediately carried to the sanitarium and Dr. M. A. Swiney made the following notes: Temperature, 98°; pulse rate, 94; respiration rate, 22. Mild condition of shock. Drowsy and restless at times; vomited twice within the first eight hours after admission. No paralyses nor sensory impairments. Pupils were equal and reacted normally. Reflexes were negative. Locally, over the upper left parietal area the scalp was contused, boggy and distinctly tender upon palpation. Treatment: For shock and the expectant palliative, quiet, external warmth (heated blankets, hot-water bottles), ice helmet, etc.

Examination. October 10, 1921, twenty-four hours after injury and admission. Consultation with Dr. Swiney. Temperature, 99.4°; pulse rate, 100; respiration rate, 22; blood-pressure, 118. Perfectly conscious, but rather confused and irritable; complains of headache. No signs of shock. Over the left parietal area the scalp is ecchymosed and edematous, associated with marked tenderness. No bleeding from nose or ears; no mastoid ecchymosis; otoscopic examination, negative. No paralyses nor sensory impairments. Pupils, negative. Reflexes, superficial: right epigastric and abdominal skin reflexes less active than left; deep: patellar increased, but equal; no ankle clonus nor definite Babinski. Fundi, negative except for a slight dilatation of the retinal veins; no edematous blurring of either optic disk. Roentgen-ray report: "Vertical linear fracture of left parietal bone, extending downward into squamous portion of left temporal bone."

No lumbar puncture was advised as the condition appeared to be simply one of fracture of the skull, with a mild associated cerebral concussion and no signs of a definite increase of the intracranial pressure or of any intracranial lesion. (It is usually better judgment to perform a lumbar puncture upon these traumatic cases after the signs of initial shock have disappeared in order to obtain the most accurate information regarding the intracranial condition, the presence or absence of a definite increase of the intracranial pressure, whether of hemorrhage or of cerebral edema, so that if a second test becomes advisable the results may be compared and thus the progress of the intracranial condition may be the more readily understood.) Treatment: The expectant palliative method

was continued and the prognosis was considered excellent in the absence of a high intracranial pressure, and especially in view of the fact that the patient was a child. The pulse and respiration rates to be noted every thirty minutes.

Upon the following afternoon (October 11, and forty-eight hours after the injury) the pulse and respiration rates became 88 and 20 respectively, the restlessness subsided and there were no complaints with the exception of a slight headache. This favorable condition continued until late in the afternoon of October 13, four days after the injury, when the pulse- and respiration-rates gradually descended within three hours to 72 and to 18, and four hours later to 60 and to 16 respectively; more drowsy, with complaints of headache and of dizziness of an objective character; the temperature and the blood-pressure remained normal. An examination at this time did not disclose any gross change in the physical condition. The child was conscious, with no paralyses nor sensory impairments, but the retinal veins of each fundus were observed ophthalmoscopically to be dilated and the nasal halves and temporal margins of both optic disks were obscured and blurred by edema; the physiologic cups were both shallow. A lumbar puncture, using the spinal mercurial manometer to estimate the pressure of the cerebrospinal fluid, recorded a marked increase—22 mm. For fear of the acute onset of the signs of medullary compression—the rhythmical Cheyne-Stokes respiration—and pulse-rates, with an increased blood-pressure of varying degree (late signs of high intracranial pressure, whether of hemorrhage or of cerebral edema alone), an immediate left subtemporal decompression and drainage were advised as being not only of much less risk of life to the patient than a continuance of the high intracranial pressure, but as offering to the patient a much greater chance of future normality —physically, mentally and emotionally.

Operation. October 14, 1921, four and a half days after injury. Left subtemporal decompression and drainage: usual vertical incision and bone removed; linear fracture passed downward to the base through this area of bone, and thus permitting an ecchymosis and edema of the muscle fibers beneath the temporal fascia (a very reliable sign of fracture of the underlying bone). Several small extradural clots. Dura bulging, tense and non-pulsating; upon incising it, slightly straw-colored cerebrospinal fluid spurted to a height of several inches and upon enlarging the dural opening, a very "wet" edematous cortex tended to protrude but did not rupture; owing to the rapid escape of a large amount of cerebrospinal fluid, the cerebral cortex began to pulsate, and soon its bulging lessened so that normal pulsation occurred. No hemorrhage nor any gross cortical lesion ascertained, only a marked condition of "cerebral edema." Usual closure with a small drain of rubber tissue at the upper and lower angles of the incision;

duration, forty minutes. Postoperative notes: Excellent operative recovery; temperature never exceeded 102°, while the pulse and respiration rates within six hours after operation became 96 and 20, and eighteen hours after operation reached and remained around 84 and 20, respectively, during the operative convalescence. There were no complaints of headache nor of dizziness. Incision healed per primam, all sutures being removed on the seventh day and the bandage on the tenth day postoperative. The operative area, however, bulged beyond the flush of the surrounding scalp, and although the pulsation was normal, yet it was considered advisable to keep the patient quietly in bed in the hope that the persisting cerebral edema would gradually lessen so that the intracranial pressure would descend to normal, and thus the operative area become depressed and sunken in—a process usually requiring about three weeks postoperative. The absorption of the excess cerebrospinal fluid, traumatic cerebral edema, did progress, but much more slowly than is usual and especially in children, so that at the delayed discharge of the patient from the hospital (forty-three days after injury) the decompression area was only slightly depressed, but with normal pulsation; the general physical and neurologic examination was otherwise negative. *Treatment:* Parents were advised to continue the patient's hospital treatment at home to lessen the condition of cerebral edema until the operative area became depressed—a quiet inactive life with no exciting games, and at least twelve hours of sleep each night and six other hours to be spent in bed; vegetable, fruit and cereal diet, with no meat and meat soup and naturally no tea or coffee; fresh fish and the white of chicken not more than twice a week; daily warm bath; bowels to move freely. (In selected cases thyroid and thymus gland may be used to diminish the secretion of the cerebrospinal fluid.) Last examination: September 6, 1922, eleven months after operation. No complaints. Operative area definitely depressed and pulsates normally; pupils, negative; reflexes, negative; fundi, negative.

Remarks. Delayed traumatic cerebral edema in a child and of degree sufficient to necessitate an operative decompression and drainage is most unusual, and especially in the absence of severe cerebral lesions, extensive subdural hemorrhage, cerebral contusions or lacerations; this case history is common in adults, particularly in the alcoholic and arteriosclerotic types of patients with or without intracranial hemorrhage, but in children it is indeed rare. The general character of the cerebral edema, without localizing signs pointing to a definite area of the brain as being involved, is also the rule in adults.

In less severe cases having a lower intracranial pressure (not above 16 mm.) repeated lumbar punctures of spinal drainage may

be used, but this method of decompression is distinctly dangerous when the intracranial pressure is high, and especially in the presence of signs of medullary compression, for fear of an acute choking of the medulla in the foramen magnum.

The comparative unimportance of the fracture of the skull is also illustrated in this case history; its presence rather aided the patient to decompress himself by permitting the escape of any hemorrhage and cerebral edema from the otherwise closed cranial cavity into the tissues of the scalp (and in other patients externally through the ears and nose), and this lessening of the intracranial pressure, together with the other means of natural absorption, frequently suffices to permit the milder cases of intracranial pressure to recover with the expectant palliative treatment alone, whereas, if no fracture of the skull were present, then repeated lumbar punctures and even a cranial decompression might be indicated to obtain not only a recovery of life but the maximum of future normality.

Rarely is the measurement of the blood-pressure of value in the early diagnosis and in the early treatment of these traumatic intracranial conditions. Naturally, the diagnosis of initial shock is confirmed by subnormal temperature and blood-pressure, associated with increased pulse and respiration rates, but to delay the rational treatment of these patients with and without a fracture of the skull until the pulse and respiration rates are markedly retarded below 60 and 26 respectively, and in the presence of edematous fundal changes, and especially with the spinal mercurial manometer registering the pressure of the cerebrospinal fluid above 16 mm. merely because the blood-pressure is not definitely increased (this is a dangerous sign of advanced medullary compression),—it has been this method of "watchful waiting" that has permitted many of these patients to pass from this preliminary stage of increased intracranial pressure into that of pronounced medullary compression, where the blood-pressure is always increased and at the great risk to the patient's life, operation or no operation.

Chronic Cerebral Edema. Within the past few years the profession has been more and more impressed with the end-results in these patients. To be sure, the preservation of life is essential, and yet the treatment of the acute condition should be not only to preserve life, but also to restore a condition of approximate normality, both mentally and physically. The attitude of the profession has largely been one of surprise if a patient with a "fracture of the skull," and particularly of the base, recovered; and if the mental, emotional or physical condition was not so normal as before the injury, "Well, he had a fracture of the skull and should consider himself fortunate to be alive." It has been this feeling of comparative helplessness that has permitted these patients to be very much neglected, it being considered that the mental and

physical impairment was due to a definite gross primary brain lesion at the time of the injury and, therefore, an irreparable condition. Fortunately, however, this is a fact in only a small percentage of the patients having had severe cranial injuries with or without a fracture of the skull, and these are the selected patients having the so-called "chronic brain injuries" that I wish to discuss here.

During the past eight years I have had the opportunity to examine and to treat a large series of patients having acute brain injuries, and it has been very impressive to note, either at autopsy or at operation, the comparative rarity of extensive cerebral laceration in these patients. It is conceded that in large compound, depressed fractures of the vault and in the occasional gunshot injuries of civil life, extensive cerebral laceration does occur and, therefore, if the patient should survive then an irreparable brain injury presents its symptoms and signs. Yet it is indeed most infrequent for gross tears in the cerebral cortex to occur in the usual cranial injuries, with or without a fracture of the vault or of the base of the skull. At autopsy upon those patients, who have died from the extreme initial shock or from an infective meningoencephalitis or from a terminal medullary edema resulting from high intracranial pressure of hemorrhage and of excess cerebrospinal fluid, the most common of cerebral lesions was a contusion of the superficial layers of the cortex of the anterior and inferior surfaces of either frontal lobe and of the tip of either temporosphenoidal lobe, but no extensive laceration, merely a bruising of these areas covered by a thin layer of localized supracortical hemorrhage. Even these findings, however, were not frequent. The most common postmortem condition was a large amount of free bloody cerebrospinal fluid associated with a layer of supracortical hemorrhagic clot of varying thickness, the brain itself being swollen and edematous, and of the so-called "wet" and "water-logged" type. This condition of supracortical hemorrhage and excess cerebrospinal fluid is also the usual operative finding, and rarely is a gross cerebral laceration exposed. The relative infrequency of large cerebral lacerations is also demonstrated clinically in those patients who make such excellent recovery of function from hemiplegia, following most severe cranial traumata with and without an operative decompression, and thus confirming the opinion that the immediate paralysis was due to local compression of hemorrhage and of cerebral edema rather than to a gross cerebral laceration. It is in those patients having high intracranial pressure, especially when it is due chiefly to hemorrhage, that the subtemporal decompression and drainage is the treatment of choice, from the standpoint not only of recovery of life, but also of the ultimate recovery of function.

We are now concerned with those patients who have recovered from the immediate effects of the acute cranial injury and yet

remain with symptoms and signs of definite impairment—severe persistent headaches, early fatigue, inability to work throughout the day as formerly, dizzy spells, a definite change of personality of the depressed or of the excitable and irritable type, and even epilepsy in its various manifestations. These are cases that form a most interesting group for study.

It is an opinion rather common among the laity and, to a less extent, in the medical profession that once an individual has had a fracture of the skull he is never the same again, if not mentally and physically, then at least in the emotional reactions; that he is more irritable, with periods of depression or of excitement, frequently complains of persistent headache, has a sense of early fatigue so that the former day's work is impossible or at least difficult, occasional spells of vertigo and at times even epileptiform seizures. Definite changes of the personality have been very frequently observed, as manifested by less interest in surroundings and ambitions for the future, and unreliability to such a degree that he is termed "a loafer and a good-for-nothing." The condition of a large percentage of those patients was called that of "post-traumatic neurosis"—a functional disturbance resulting from the "shock" of the injury, "concussion" of the brain, etc., while the condition of the smaller number of these impaired patients was considered as being due to a gross organic injury of the brain at the time of the accident, such as cerebral contusions and lacerations associated with hemorrhage of varying degree. In the absence of macroscopic lesions to be observed with the naked eye, then the condition was believed to be due to minute and possibly microscopic changes, not only in the cortical nerve cells themselves, but also in their interrelationship and associated nerve tracts, and thus an irreparable condition.

With this post-traumatic condition in mind, in 1912, I attempted to ascertain the status of those patients at three of the large hospitals in New York City, who had had a "fracture of the skull" during the preceding decade of 1900–1910. The mortality of the acute condition was 46 to 64 per cent, while the operative mortality itself was 87 per cent; this latter was due chiefly to the type of operation performed, usually an extensive osteoplastic flap exposure, and the frequent performance of the operation during the initial stage of extreme shock or during the terminal stage of medullary edema. Under these conditions, Pearce Bailey was undoubtedly correct in the belief then, that these patients "get along just as well without as with operation." Of the total patients who were discharged from those three hospitals as "well," "cured" or "improved," I was successful in locating only 34 per cent, but of this number 67 per cent were still suffering from the effects of the former injury, the chief complaints being headache, early fatigue, change of personality and, in a very small number, con-

vulsive seizures. The records of these impaired patients were very instructive, in that their hospital residence was usually longer than that of the other cranial injury cases by a number of days and even of weeks, while frequent notes were found of prolonged stupor and even of unconsciousness, of severe headache and of retarded pulse rate—symptoms and signs indicative of an increased intracranial pressure; rarely was an ophthalmoscopic examination made and even more rarely had a lumbar puncture been performed. In examining these chronic cases, I was very much surprised to find in a large number of them the definite evidence of an increase of intracranial pressure, as observed with the ophthalmoscope and particularly with the estimation of the pressure of the cerebrospinal fluid at lumbar puncture. Upon 9 of these selected patients the operation of subtemporal decompression and drainage was performed, even at this late date following the injury, and the operative findings were all similar, no gross cortical lesions exposed, but a "wet," swollen edematous brain under varying degrees of increased pressure; along the supracortical veins in the sulci, however, was a cloudy induration of new tissue formation surrounding the vessel walls, which were also thickened. Microscopic sections have now been made of this condition occurring in similar patients and also in children who have had a supracortical hemorrhage at the time of birth; this tissue formation is now recognized as the organization residue of connective tissue of a former layer of supracortical blood, which had collected chiefly in the sulci about these veins and thus had blocked the little stomata of exit of the cerebrospinal fluid through the walls of these vessels—the main channels of excretion of the cerebrospinal fluid into the blood stream. In this manner, a mild condition of external hydrocephalus had been produced by this partial blockage of the excretion of the cerebrospinal fluid.

Microscopic sections of the cortical cells and their normal arrangement have only rarely disclosed a definite change of structure, although this added complication cannot be excluded in any case. It is the pathologic condition, however, about the supracortical veins that has been overlooked in the past; and it has only been since we have learned that over 80 per cent of the excretion of the cerebrospinal fluid occurs through the supracortical veins lying in the sulci, that it was recognized that this condition of new tissue formation following the hemorrhage was the main lesion in causing the edematous brain, due to the partial blockage of the excretion of the cerebrospinal fluid with the resulting varying degrees of intracranial pressure. Those patients making excellent recoveries with the expectant palliative treatment alone, and over 50 per cent do, undoubtedly are the ones in whom the natural means of absorption have been sufficient to take care of the free supracortical blood, so that no real residue or new tissue formation results, since practi-

cally all of the hemorrhage has been absorbed. I have had the opportunity to demonstrate the confirmation of this opinion in 3 patients who had had cranial injuries with a resulting intracranial hemorrhage, as indicated by the bloody cerebrospinal fluid at lumbar puncture, which was not sufficient, however, to produce a marked increase of the intracranial pressure, so that the expectant palliative treatment alone was indicated in order to obtain an excellent recovery. Later, upon death from other causes, autopsy in these 3 cases disclosed little, if any, new tissue formation about the supracortical veins in the sulci, the hemorrhage having been entirely absorbed. The brain was not edematous, there being no blockage of the excretion of the cerebrospinal fluid.

These chronic patients having had an intracranial injury, and most probably a supracortical hemorrhage, with or without a fracture of the skull, who have not recovered their former normality and in whom headache, early fatigue, change of personality or even convulsive seizures persist, should be most carefully examined from the standpoint of the presence or absence of an increased intracranial pressure, as found in the fundi with the ophthalmoscope and, more accurately still, by the spinal mercurial manometer at lumbar puncture. If no increase of the intracranial pressure is present, then the treatment can be only of the expectant palliative type because the intracranial damage has already occurred, whether due to a primary gross or to a minute microscopic lesion of the cortical cells or to a prolonged high intracranial pressure, which has gradually become lowered as a result of the atrophy of the cerebral cells—a permanent impairment, being a compensatory lowering of intracranial pressure at the expense of the brain itself. But if a definite increase of the intracranial pressure persists in spite of the usual medical expectant palliative treatment, then the patient can be greatly benefited and improved by means of an early subtemporal decompression and permanent drainage of the blocked cerebrospinal fluid. The dura should naturally be opened widely and permitted to remain open and not resutured, otherwise the decompression and drainage is of only temporary value. Excellent results have been obtained in this class of patients and the earlier the condition of increased intracranial pressure can be lowered to normal, just so much more of an improvement can be expected from the operation; naturally, in those chronic sclerotic patients, greatly deteriorated during a period of years, even to the degree of dementia, little, if anything, can be expected at this late date.

In closing, let me merely mention the similar chronic condition occurring in children as the result of an intracranial hemorrhage at the time of birth, most frequently in difficult labor, with or without instruments. They are usually first children, and unless convulsive twitchings occur within several days after birth, or the

child is abnormally excitable or stuporous, the condition is commonly overlooked and the baby may be considered a normal child until the seventh or eighth month, and even later. Then it is observed that the child is not holding up its head, and later does not sit up or attempt to stand until months after the normal time; convulsive twitchings may or may not be present; speech is usually retarded,—in fact, the entire physical and mental activities are delayed and retarded in varying degree. If examinations now show a marked increase of the intracranial pressure, these are the selected patients who can be greatly benefited by subtemporal decompression and permanent drainage of the blocked cerebrospinal fluid, even at the late date of several years following the injury, just as in the chronic brain injuries occurring in adults. However, the ideal treatment of these conditions of intracranial hemorrhage is at the time of the acute condition—within the first few days following birth in the baby, and within a period of hours following the injury in adults. In these new-born babies, if repeated lumbar punctures with removal of large amounts of blood cerebrospinal fluid do not suffice to lower permanently the increased intracranial pressure, then a modified subtemporal decompression and drainage operation is immediately indicated, just as in the acute brain injuries of adults having the symptoms and signs of high intracranial pressure. Infants surviving a birth hemorrhage, whose increased intracranial pressure has not been lowered to normal, cannot develop as they should, either mentally or physically; as a result of this condition, these patients are eventually added to that large group of spastic and defective children—the bane of the pediatrist, orthopedist and neurologist. After a lapse of years, however, the selected children having an increased intracranial pressure can be only improved by the operative lowering of the pressure. I have now operated upon 572 of these children out of 5000 cases personally examined, of ages varying from five hours to twenty-three years, and I may state that the lesion is practically the same as occurs in adults from cranial injuries with a supracortical hemorrhage; the persistent increase of intracranial pressure is due to the partial blockage of the excretion of the cerebrospinal fluid by the connective-tissue formation resulting from the supracortical hemorrhage about the veins in the sulci, producing the characteristic "wet," edematous condition of the brain.

Conclusion. It is only in those patients having a definite increase of the intracranial pressure that any improvement can be afforded by means of the cranial decompression and drainage. Naturally, if minute sclerotic changes have taken place in the cortical cells themselves, then an irreparable damage has occurred, and even if the increased intracranial pressure is lowered to normal by operation, these advanced patients cannot make a complete recovery of function, although the relief of the pressure should improve their condition.

It is, however, in those early patients in whom the increased pressure, resulting from a partial blockage of the excretion of the cerebrospinal fluid, is the main pathologic condition, and especially in those who have no organic cellular changes, that the operation of subtemporal decompression and permanent drainage affords the greatest ultimate improvement and, in the more fortunate ones, even an apparent recovery of function.

THE PROGNOSIS IN CANCER OF THE BREAST.*

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The prognosis in cancer of the breast may be said to depend upon four factors: (1) The surgical removal; (2) the variety of the cancer; (3) the immunity of the patient; (4) the duration of the disease before operation. This paper is concerned with an evaluation of these factors, especially what variations in each are possible or to be expected, and what influence there will then be upon the prospect of cure.

The Surgical Removal. The beginning of the surgical cure of breast cancer can be said to date from 1867, when Moore asserted that cancer was a purely local disease, curable by local eradication. From 1870 to 1880 Danish, German and Austrian surgeons were the only ones to grasp this principle, and they alone reported cures, 9 per cent.

From 1880 to 1894 various isolated surgical principles for malignancy of the breast were formulated. Volkman advised removal of the axillary glands; Gerster advised wide excision, and gentleness in handling, stating that pulling on retractors, hooks, and so on, forced cancer cells into the lymphatics. Heidenhain traced lymphatic spread underneath the pectoralis major and advised removal of this muscle. The pectoralis major was sometimes removed, both muscles only rarely, the axilla only partially cleaned out, and the operation was frequently done in two stages. With these procedures various operators reported 20 to 25 per cent of cures, but some with wide experience stated that they had "seen cartloads of breasts removed without a single cure."

In 1894 Halsted and Willy Meyer described the present-day radical removal and advocated this technic in all cases: the extirpation of the entire contents of the axilla, removal of both pectoral muscles and the breast in one complete block; the excision

* From the Surgical Service of Dr. Max Ballin, Harper Hospital. Dr. Carl Gaines assisted in part of this work.

of all suspected tissues with the widest possible margin, in one unentered and little manipulated mass. Cures jumped to 40 to 45 per cent. Since this milestone in technical progress there have been only slight modifications in methods (the Rodman incision, the Jackson flap, Handley's wide excision of fascia), and, as a general statement, the limit of improvement in operative technic has been said to have been reached. This is reflected in the fact that Halsted's and Willy Meyer's results published in 1904-5 are essentially those of the present day, 40 to 45 per cent cures is still the average figure. Radium and the roentgen-ray have won definite places as adjuncts to surgery. In some series they have increased the percentage of cures and they uniformly inhibit local metastases. How much more cancer we will cure by perfected ray and radium methods is problematical; certainly there will be some increase, but probably there will be no radical change.

The operation then has been quite well standardized, and as a factor in prognosis will probably not be found to vary markedly in the future. The extensive cautery excision recently described by Percy[1] may prove to be another exception. No results were published, however, and the procedure has not, as yet, become generally adopted.

The Variety of the Cancer. The importance of the variety or type of the cancer when determining the prognosis, has been emphasized repeatedly. (Halsted,[2] Bloodgood,[3] and Ewing,[4]) "Scirrhous cancer represents only a part of what has existed. The struggle against cancer cells, resulting in fibrous tissue production, is not always futile, and when minute foci of cancer epithelium have been destroyed, the new fibrous tissue may, in part, be absorbed also. Thus scirrhous disease may be active and metastases take place a long time before the visible, or palpable tumor is developed." (Halsted).[2] Cases such as these may show only neuritis, paraplegia, then paralysis, in spite of careful examinations. Finally a small scirrhus of the breast will be felt and the roentgen ray show spinal metastases.

Medullary, encephaloid, or simplex, are clinical terms designating the average soft cellular tumor with very little stroma and small active cell nuclei. There is rapid progress, early skin invasion, extensive dissemination, and early cachexia.

Certain rare forms, colloid cancer, for example, tend toward encapsulation and may grow to enormous size without invading the axilla. Other types, as acute carcinosis, cancer cysts, may be rapidly fatal, occasionally in less than two months.

[1] Surg., Gynec. and Obst., 1921, **33**, 417.
[2] Tr. Am. Surg. Assn., 1907, **25**, 61.
[3] Diagnosis and Treatment of Borderline Pathological Lesions, Ann. Surg. 1913, **58**, p. 282.
[4] Neoplastic Diseases, Ed. 2, 1922.

Adenocarcinoma has been credited with a very high percentage of cures. A recent study by Bloodgood[5] raises the question of whether many of these cases are cancer at all. Seventeen cases diagnosed adenocarcinoma were in reality benign non-encapsulated adenomata, and, of course, if added to total cured cases markedly increased the percentage.

The Immunity of the Patient. As the lymphatics are invaded, especially the axillary glands, there is a tendency for previously slowly growing tumors to approach the cell type of the rapidly growing forms with correspondingly increased virulence.

An immune mechanism against cancer undoubtedly exists in the lymphatic elements of the blood. In experimental cancer a failing cancer graft is absorbed by mononuclear cells, and a lymphocytosis, a "lymphocytic crisis," marks the triumph of the body defence and the death of the graft. If the lymphoid tissue is destroyed by roentgen-ray, the animal's susceptibility to cancer is increased. If the lymphoid tissue, instead of being destroyed, is stimulated by a smaller roentgen-ray exposure, the immunity of the animal is markedly increased. (Murphy and Norton.[6])

Similarly J. W. Vaughan[7] states that early malignancy shows an increase in the large mononuclear blood cells. When these cells decrease, and the polynuclear elements increase, the tumor is growing rapidly. Then, and only then will metastases take place. He has used this differential blood count as an index of operability. However, the disturbance causing polymorphonuclear leukocytosis can be brought about by so many other factors than the spreading of cancer, that it is difficult to gauge operability from relative leucocyte percentages.

McCarty[8] has shown in his studies that the prognosis in cancer of the breast is dependent on factors analogous to the variety of the tumor and immunity of the patient. The more closely the tumor type resembles the embryonic cell, the more virulent is the growth. Vice versa, if the cell shows marked differentiation from the primitive, the growth is much more benign. Breast cancers showing cellular differentiation had 57 per cent greater postoperative length of life than the normal average of the group studied. He also measured the prognostic value of the defense pictures seen about the tumor, lymphocytic reaction, fibrosis, and hyalinization. Patients showing all of these reactions had 37 per cent greater expectancy than the normal average, and 42 per cent greater expectancy than if none of these factors were present.

What relative importance the patient's immunity is in determining the ultimate outlook, as contrasted with the type or variety

[5] Arch. Surg., 1921, **3**, 527.
[6] Science, 1915, **42**, 842.
[7] Jour. Am. Med. Assn., 1917, **49**, 1952.
[8] Ann. Surg., 1922, **75**, 61.

of the tumor, is problematical. If the cell type changes as the tumor progresses, is this simply an index of lowered resistance, or is the cell metamorphosis primary? Does a cancer begin as a scirrhus rather than a medullary form because one patient has a greater immunity, with more tendency to fibrous tissue formation, or does the type of growth determine the tissue reaction? It is apparently the same enigma met with in infection and resistance, the pneumococcus strain against the body defence.

Practically, however, these considerations are important as follows: a rapidly growing type, unless treated almost as an emergency disease, and with extensive radical removal, is hopeless (Fig. 1). Secondary operations are of no avail. The patient lives longer without them. Another type may be cured by incom-

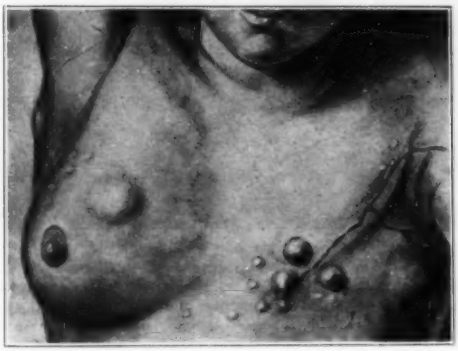

FIG. 1.—Case I. Advanced medullary carcinoma. Appearance five months after radical amputation of left breast. Operation was performed five months after tumor was noted. Axillary glands were badly infected at that time. Three months after operation metastases appeared in left side of neck and in the region of the scar. Soon there was edema of the arm, numerous skin metastases, and symptoms of abdominal metastases with death six months after operation. To offer any prospect of cure such a case must almost be considered as an emergency disease.

plete removal. Metastases may be resected, sometimes repeatedly and with good result. (Fig. 2—an extensive local metastasis was removed by a cancer fakir by means of arsenic paste). Willy Meyer has stated that statistics of cures in cancer of the breast are worthless as regards the prognoses in an individual case, because the cure depends so much on the virulence of the tumor.

The Duration of the Disease before Operation. Cancer radiates in a sphere; on the surface, growth is expressed in square dimensions, not as linear increase. Consequently, doubling the time increases the risk of recurrence not twice but two to the square dimension or four times. (E. Wyllis Andrews[9].) If a tumor has grown to a certain size in two months, after two more months have elapsed,

[9] Ann. Surg., 1905, **42**, 903.

the probability of a cure is not one-half, but one-fourth. When the axilla is free from disease, the prognosis is generally stated to be about 80 per cent cures (Crile 80 per cent; Johns Hopkins 85 per cent). When the axilla is involved, the prognosis for cure ranges from 25 per cent (Halsted, Rodman) to 12 to 14 per cent (Massachusetts General and Crile) and in some cases as low as 4 per cent.

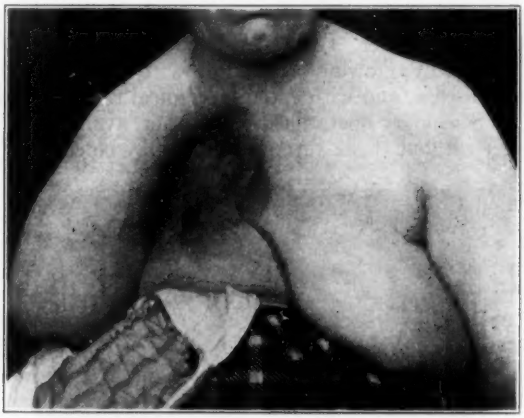

FIG. 2.—Case II. Extension locally only. Repeated removal indicated. April, 1919, radical removal of right breast. A lump 2 cm. in diameter in the outer upper quadrant, had been present four months. Three months after operation a tumor was noted in the neighborhood of the right second and third ribs anteriorly. May, 1920 there was a two-fist size local recurrence, attached to the clavicle and thorax, and firmly fixed in Mohrenheim's fossa. Three surgeons independently pronounced it inoperable. Not satisfied, the patient consulted a cancer quack (June, 1920), who made daily applications of arsenic paste, each day clipping off the dead eschar before reapplying the caustic. After five months of this treatment, the anterior thoracic wall, the right clavicle and apparently the growth were destroyed. In October, 1920, there was sudden profuse hemorrhage from the axillary vessels, which stopped spontaneously in thirty minutes. One week later the forearm was gangrenous and had to be amputated above the elbow. November, 1920 the necrotic remnants of the right clavicle, right second and third ribs were removed, and skin grafts placed directly over the lung tissue. There was no evidence of recurrence. April, 1921, a local recurrence was excised from the region of the fourth costochondral junction. This was followed by a severe attack of erysipelas. July, 1921, a similar local recurrence was excised, roentgen-ray still showing the thorax clear of metastases. (The photograph was taken the day before the operation). Thus, two and a half years after its initial appearance, a carcinoma showed no thoracic involvement in spite of continuous local growth. Repeated removal was certainly indicated.

Of the cases coming to Harper Hospital from 1914 to 1920, 80 per cent already had metastases in the axilla: in only 20 per cent was the axilla clinically free. That is, when adequate treatment was first instituted, four-fifths of the patients had three in four chances of succumbing; one-fifth had three in four chances of cure.

What is early? This question perplexed no less a student of cancer than the late J. B. Murphy. The small circumscribed

carcinoma, or the microscopic cancer metamorphosis may have 100 per cent chance of cure, and may even have that prognosis with incomplete removal; the fully developed carcinoma may within the space of a very few weeks become hopeless. If one accepts Handley's view that cancer spreads along the fascial lymphatics as a gigantic ringworm, far in advance of any demonstrable deposits, how early must surgical intervention take place to regularly establish a cure?

We may never have an answer to this question, chiefly because different cancers progress with different degrees of rapidity depending on the patient's immunity and the type of the tumor. One is encapsulated for months and then suddenly bursts forth into a very malignant tumor; a scirrhus may grow very slowly, but the defence of the organism may hold the primary as well as multiple secondary growths in check for months or years. There have been well authenticated cases of spontaneous disappearance. On the other hand patients with certain virulent cellular growths (so-called acute carcinosis) may be doomed almost from the start. (Fig. 1.)

The axillary glands are uniformly involved within twelve months, and then the prognosis is 25 per cent to 12 per cent cures, as above stated, whereas a few months before the same case had 80 per cent chance of cure.

If we cannot exactly define early, we can continue exhorting earlier diagnosis and operation. The probability is that cancer must in a certain percentage of cases be treated as an emergency disease if the surgical intervention is to take place soon enough to allow of radical removal beyond the involved area.

Women are surely coming sooner for operation than formerly, and this decrease in the time factor is a most hopeful and promising sign. Where increasing percentages of cures have been reported in recent series, the increase has often been ascribed to the inclusion of a greater number of early cases rather than to improvements in technic. Bloodgood's[10] data show the following interesting facts: At Johns Hopkins, from 1890 to 1915, the proportion of benign lesions of the breast has risen from 32 to 59 per cent of the total number of breast tumors coming to operation. The percentages of borderline cases, where the surgeon is in doubt regarding the gross nature of the lesion has risen; whereas formerly there was 10 per cent error in these cases, now the error is 15 per cent. Fully developed carcinoma of the breast has decreased from 90 per cent of the total in 1890 to 78 per cent in 1913.

The following table compiled from admissions to Harper Hospital during the years 1914 to 1920, likewise shows a slow but significant steady decrease in the time factor.

[10] Jour. Am. Med. Assn., 1916, **66**, 552.

AVERAGE DURATION OF TUMOR BEFORE OPERATION. (PATIENT'S STATEMENT.)

1914	16.5 months
1915	13.4 months
1916	17 months
1917	15 months
1918	14 months
1919	13 months
1920	10 months

Of the factors upon which the prognosis of a given case of carcinoma of the breast depends (the surgical removal, the immunity of the patient, the variety of the tumor, and the duration of the disease before operation), the last, the duration of the disease before operation, is the only one capable of any wide variation at our hands.

The ever widening realization of this fact, the popular spread of Bloodgood's doctrine that "the cure of cancer is its early recognition," will do more to change the percentage columns of cancer statistics than anything known to medicine today.

Conclusions. 1. Radically different methods of surgical removal of breast cancers are not to be expected. Improved operative proceedures will play little role in increasing the percentage of cures. 2. The clinical variety of the tumor, or the variety divided by the patient's immunity, is of profound importance in determining the prognosis. 3. Operations upon recurrent carcinoma of the breast are distinctly indicated in certain cases, when the type is favorable. If the type is not favorable, operation hastens death. 4. Eighty per cent of admissions to Harper Hospital already had axillary involvement. When the axilla is involved the prognosis is 4 to 25 per cent cure; uninvolved the prognosis is 80 per cent cure. 5. There is substantial evidence that in breast cancer women are seeking advice and operation earlier than formerly, but in this matter it may be said that the surface only has been scratched. 6. Since the time factor is capable of such wide variation at our hands and is capable of such influence upon the ultimate prognosis, our best efforts should be directed toward reducing the interval between appearance and eradication, toward transposing "80 per cent with axillary involvement" to "80 per cent clinically benign." This will be realized only when popular information is so widespread that every woman regards a lump in her breast with dread suspicion as soon as, and not six months after, she first perceived it.

MAGNESIUM SULPHATE AS A SEDATIVE.

By Paul G. Weston, M.D.

and

M. Q. Howard, M.D.

Warren, Penna.

In a series of papers in the *American Journal of Physiology* beginning in 1904, Meltzer and Auer reported the action of magnesium sulphate when injected subcutaneously or intravenously. They found that the "primary effect of magnesium upon the nerve cells is that of paralysis without any preceding excitation. The effect seemed to be exclusively of an inhibitory character." They also noted that calcium antagonizes the abnormal activity of its three inorganic associates in the animal body, sodium, potassium and magnesium, be the activity an over-inhibition or an over-excitation. In one of their experiments a rabbit was given sufficient magnesium sulphate solution to cause complete muscular paralysis. The intravenous injection of a very small amount of calcium chloride caused this paralysis to disappear at once. Based on the fatal dose for rabbit, the fatal dose for a man weighing 75 kg. (165 lbs.) would be approximately 120 gm. (4 ounces) given hypodermically.

It occurred to us that since magnesium sulphate has such a paralyzing action on the nerve cell, it should be of use as a sedative in excited states, inasmuch as the toxic dose is very high and the antidote prompt in its action. We have therefore been using the salt as a sedative for a little over two years and our results are here recorded.

Preparation of the Salt. The crude magnesium sulphate of the apothecary shops is recrystallized three times and a perfectly pure product obtained. It was found that C. P., U. S. P. and "reagent" magnesium sulphate were quite impure and none would give a clear, colorless solution. It cannot be stated whether these impurities are toxic or not, for only pure salt was used in our cases.

A 50 per cent solution of the salt with its water of crystallization was made in distilled water and sterilized in the autoclave. The solution was dispensed in 50 or 100 cc bottles closed with a rubber stopper having a thin rubber diaphragm in its center, such a stopper as is used in bacterin bottles.

The usual dose was 2 cc of the 50 per cent solution. It was injected subcutaneously or intramuscularly, the usual aseptic technic being employed. No local pain and no sloughing followed the injections. The dose was repeated at half-hour intervals when necessary. At first a 25 per cent solution of the salt was used and the results with mildly excited patients were very satis-

factory; but it was so often necessary to repeat this dose for more excited patients that we changed to a 50 per cent solution and have used this strength regularly.

For convenience we have placed the patients in the following arbitrary groups:

Group 1. Patients who remained in bed talking quietly to themselves in response to hallucinations. They did not awaken or annoy other patients in the same ward and did not sleep.

Group 2. Patients who remained in bed talking loudly and frequently shouting or screaming. They annoyed the other patients and awakened the sleeping ones.

Group 3. Patients who persisted in getting out of bed and annoying other patients who were sleeping. They were excited, walked up and down the floor and shouted. They could not be persuaded to remain in bed.

Group 4. Patients who showed the same general reaction as those of Group 3 but were more excited and noisy.

Effects of Magnesium Sulphate. Group 1. Nine patients; all responded readily and slept from five to seven hours.

Group 2. Twelve patients; 11 responded readily; 1 patient showed no effect after the injection of three doses.

Group 3. One hundred and fifty-eight patients; 128 of these responded to one dose of 2 cc and 10 after two doses. Twenty patients, 12.6 per cent, failed to respond to three or more doses.

Group 4. Twenty-four patients; 20 of these responded after one dose and 2 after two doses. Two patients were unaffected by three or more doses.

Most of the patients went to sleep in from fifteen to thirty minutes after the salt had been injected. A small number did not sleep but remained quietly in bed. One of these was an old morphin addict. She was well aware that she had been given some drug that she had never had before but a good description of her subjective sensations was not obtainable. Many of the patients required a sedative each night for varying periods of time. Of those who reacted to the salt the first time it was injected, all but one reacted to subsequent injections. This one received an injection of 2 cc on each of two succeeding nights and slept six hours each time. Six months later when she had a second attack of excitement, the salt had no effect whatever. Within two and a half hours she was given 15 cc of the solution, representing $7\frac{1}{2}$ gm. of the salt but no effect was observed. The excitement of the second attack was apparently of the same degree as the first. In two other instances 15 cc of the solution were injected during two and a half hours with no apparent effect.

The pulse rate was determined before and every half hour after the injection for a period of three hours. In no case in which the pulse rate before the injection was not over 72 was there a dimi-

nution of more than 5 beats per minute. In those cases in which the pulse rate was over 80, the decrease was more marked, 8 to 12 beats, but the decrease was only that which occurs physiologically when a person is asleep or resting quietly in bed. In short, there was no change in pulse rate due to the magnesium. Meltzer and Auer emphasized this point in their papers. The duration of the sedative action was from five to ten hours.

We have used the salt in a number of persons, not insane, who were suffering from severe pain. The results were very gratifying. The anesthetic effect was quite marked and in 2 cases the pain was so severe and protracted that the continuous use of morphin would almost surely have led to the formation of a habit. In both these cases salicylates and morphin had previously been used.

After we had been using magnesium sulphate for some time, the paper of Gwathmey[1] appeared in which he recommended giving morphin in a 25 per cent solution of magnesium sulphate to prolong the action of the morphin. We had found that in cases not quieted by 6 to 10 cc of 50 per cent magnesium sulphate solution, morphin also was of no value except in heroic doses, and that when the magnesium sulphate alone failed to give relief, it was of no effect when used in combination with $\frac{1}{4}$ gr. of morphin.

Summary. Pure, recrystallized magnesium sulphate with its water of crystallization was made into a 50 per cent solution with distilled water and sterilized. The solution was injected subcutaneously and intramuscularly more than a thousand times. No local pain or sloughing occurred when proper aseptic technic was used. In 82.7 per cent of the cases the sedative action was prompt, the patient becoming quiet after fifteen or thirty minutes and sleeping from five to seven hours. In a few instances the patient became quiet but did not sleep. The effect persisted for from five to ten hours. The salt was found to be a very excellent substitute for morphin and hyoscin in many cases. It was found necessary to repeat the dose of 2 cc in 6 per cent of the cases before sedation was obtained. In 11 per cent of the cases no effect at all was noticed after the injection of three or more doses. The salt is quite harmless in the dose necessary to produce sedative effect and can be given liberally when necessary. No opportunity has presented itself for using the salt in preoperative or postoperative cases or in acute thyrotoxicosis.

[1] Jour. Am. Med. Assn., 1921, **76**, 22.

NEPHRITIS: AUTOPSIED CASES AND RECENT VIEWS.

By Rolfe Floyd, M.D.,
NEW YORK.

The French school believe in a dissociation of function in renal diseases—difficulty in eliminating salt in one type; difficulty in eliminating nitrogenous waste in another. While this dissociation is probably frequent in early stages, the cases as we meet them in the hospital wards usually show a failure of both salt and urea elimination; that is, they have retention both of salt and nitrogen.

That fatal azotemia may occur in pure type is shown by the following case which died on my service at Roosevelt Hospital and on which I performed the autopsy.

Case I.—*Fatal Azotemia.* Woman, aged thirty-six years. General health said to have been good; no renal symptoms. Miscarried at six weeks, on July 13, 1921. Curetted at Roosevelt Hospital on July 16. After operation she became jaundiced and vomited; the jaundice cleared but the vomiting persisted until, on July 21, she was transferred to the medical service. She was much prostrated. Her heart, lungs and abdomen were normal. Her tongue was dry; reflexes normal; no edema. Blood-pressure: 118 systolic, 80 diastolic. Hemoglobin, 70 per cent; red cells, 4,920,000; white cells, which had been 44,000 with 94 per cent polynuclears on July 16, had fallen to 8400 with 68 per cent polynuclears on July 21, but later rose to 21,400 with 87 per cent polynuclears on July 29. A spinal puncture resulted in a dry tap.

Five examinations of her urine were made on the gynecological service. The specific gravity varied between 1015 and 1025; a trace of albumin was always present, but no casts. One examination after her transfer to my service showed specific gravity 1020; no albumin or sugar; no casts.

She was put on a Murphy drip and teaspoon doses of milk by mouth. The vomiting diminished; the rectum, however, became intolerant and the drip was discontinued.

An acute and painful parotitis developed the day after the transfer and lasted a week, interfering with taking fluid or food by mouth and retarding her progress.

An intense general erythematous eruption, simulating that of severe measles, appeared on July 27, just as the parotitis was subsiding. This faded in three days. By this time she was taking and retaining a fair amount of fluid and some nourishment by mouth.

Her blood chemistry was reported on July 30 to be nonprotein nitrogen 539, urea nitrogen 293, creatinin 12, uric acid 14.3, sugar 18. All these figures and those appearing later in this paper indicate milligrams in 100 cc of blood serum.

On July 31, she became stuporous and sank into coma. On August 2, she died.

Autopsy. The autopsy was done eight hours after death and included examination of the brain.

The heart was not enlarged, weighing 330 gm.; its valves and wall were normal.

There was no significant lesion anywhere except in the kidneys.

The kidneys were slightly large, weighing 330 gm. Their surfaces were smooth, capsules free, their color decidedly lighter than normal. Cortex of normal thickness but with obscure markings.

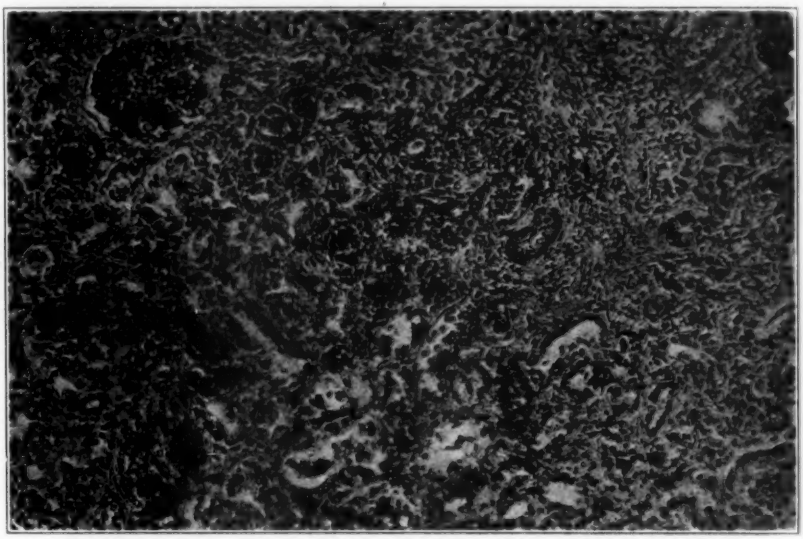

FIG. 1.—Kidney in pure azotemia. The dark bodies in some of the tubes are blood casts. × 133 and reduced.

Under the microscope there is a decided and general increase of the connective tissue in the cortex. There is a marked swelling of the tubular epithelium. The lumina of the tubes, which are narrowed by this swelling, contain red cells and some hyaline and blood casts. The glomeruli show much less pathological change than the tubes and stroma. Many of them are normal, but many others show a definite increase of tuft cells, obscuring the outline of individual loops. There are a few round-cell foci at the junction of cortex and medulla. There is no sclerosis of the arteries (Fig. 1).

Comment. Volhard and Fahr[1] consider hypertension an "obligatory" result of nitrogenous retention except in advanced tuberculosis or pronounced alcoholism. Tension they say may fail with failure of

[1] Die Brightsche Nierenkrankheit, Mannheim, 1914.

heart power, but then a cardiac hypertrophy will be found at autopsy. This case is entirely at variance with their view and they evidently had not seen one like it when they wrote (1914).

On the other hand the case demonstrates the correctness of the view held by Widal and Ambard[2] that in disease one of the renal functions may fail without the others.

So far as my own experience goes the case is unique. The sudden development of uremia in this woman without premonitory renal symptoms was probably due to the low urinary volume incident to reduced fluid intake. Normal kidneys can concentrate the urine to the point where about 500 cc a day can carry off the urea that must be excreted during the 24-hour period in order to prevent retention. Damaged kidneys cannot concentrate urea so much and, depending on how weak this power, 1000 cc, 1500 cc, even more will be the smallest urinary volume that can prevent urea retention. This woman probably did not pass over 600 cc, and a resulting residue of urea retained each day in her blood thus rapidly raised the total. Ambard has especially insisted on this cause of retention.

Had I adequately realized this danger I might have obviated it by introducing fluid beneath her skin or in her veins. If, however, the kidneys had reached the point where they were incapable of excreting enough urea to keep the blood concentration below the fatal point, no matter what the urinary volume, no such plan of treatment would have been effective.

Nephrosis as a disease entity is especially insisted on by Volhard and Fahr, who define it as follows:

We have found with the same "parenchymatous picture" two types, one with increased blood-pressure and one without, and this distinction has been found to correspond to an anatomical difference. In the gross, "large white kidneys" are found both without and with increased blood-pressure, and this has led to the false conclusion that large white kidneys were all the same lesion, and the blood pressure an unessential complication. When the blood-pressure fails, so do the evidences of inflammation, viz., hyperemia, stasis, exudation and proliferation. In this group degeneration of the epithelium is the essential change, the stroma and bloodvessel changes sinking far into the background, though when fully established, they do show leukocyte infiltration as well as stroma increase. Unquestionably these inflammatory changes, because of their meagreness and their absence in fresh cases, are to be regarded as secondary and stimulated, as Weigert interprets them, by the products of cell degeneration and as a replacement fibrosis that finally reaches a large diffuse development and may lead to contraction.

If now we turn to inflammation and its primary vascular changes

[2] Physiologie normale et pathologique des reins, Paris, 1920.

it is evident that these must be present in and characterize any true nephritis. The degeneration cases in which inflammatory changes fail can then be called nephrosis in contradistinction to the inflammatory ones.

The evidences of nephritis are increased blood-pressure and blood in the urine, and, under the microscope, an inflammation of the glomeruli as well as extensive epithelial degeneration, which is common to both types of large white kidney and on which extensive dropsy chiefly depends.

The waxy kidney has been described as a separate type of disease, but it has been noted how often it gives the clinical picture of nephrosis without cardiac hypertrophy, retinitis or uremia. We do not believe that a typical amyloid kidney can be differentiated from nephrosis without amyloid. We therefore regard it as an unessential complication of nephrosis and regard both epithelial and vascular changes as due to the same cause. The same conclusion holds for the contracted nephrotic kidney with and without amyloid. Amyloid changes in no way alter the symptoms. For these reasons the amyloid kidney as a separate entity is omitted from the classification."[3]

I have always questioned the validity of this conception of Volhard and Fahr, and have expressed my doubts in an article[4] comparing their classification of Bright's disease with that of Delafield.[5] The following case has helped to confirm my skepticism.

CASE II.—*Symptoms of Nephrosis; Lesions of Nephritis.* Man, aged thirty-seven years; a cook. First came to Roosevelt Hospital in July, 1919. He had been a drinker. For one year he had been short of breath following a pleurisy; for two months there had been dropsy of the legs; for three weeks vomiting. There were physical signs at both apices confirmed by roentgen ray, and tubercle bacilli were found in the sputum. His urine varied in gravity from 1010 to 1024; it contained large amounts of albumin and many casts. His nonprotein nitrogen was 26.9. His Wassermann was positive.

He was much improved by hospital care and went to work on a farm for six months. He then considered himself cured and resumed his work in this city as a cook. He has been short of breath ever since 1919.

His second admission to the hospital occurred March 28, 1921. Three weeks prior to admission he caught cold and began to cough and expectorate. For ten days there had been rapidly increasing dropsy of the legs and swelling of the abdomen. He was having two or three liquid stools a day.

[3] This quotation is not a *verbatim* translation. It is both abbreviated and free, but an accurate statement of the authors' views so far as I comprehend them.

[4] Floyd, R.: Two Classifications of Bright's Disease, Med. Rec., April 2, 1921.

[5] Lectures on Practice of Medicine with Cases and Charts, New York, 1903.

His face was waxy white and much swollen; there was extensive subcutaneous dropsy and fluid in the abdomen. There were signs of tuberculosis at the right apex, of general bronchitis and of fluid at the right base. Three examinations showed no tubercle bacilli in the sputum.

The heart was not enlarged. Blood-pressure: 120 systolic and 62 diastolic. Wassermann negative. Hemoglobin, 80 per cent; red cells 4,600,000; white cells 15,200, with 77 per cent polynuclears.

Five urine examinations resulted as follows:

Specific gravity.	Albumin.	Sugar.	Microscope.
1050	Boiled solid	None	Many hyaline and granular casts.
1038	" "	"	" " " "
1031	" "	"	" " " "
1030	" "	"	" " " "
1028	" "	"	" " " "

The blood chemistry showed nonprotein nitrogen, 29.8; urea nitrogen, 13.5; creatinin, 0.98; uric acid, 2.4; sugar, 0.1; chlorides, 6. In the plasma there were 3.79 per cent of albumin and 5.61 per cent of globulin.

The phenolsulphonephthalein test, done twice, resulted as follows:

1st hour.	2d hour.	Total.
36	23	59
20	15	35

The nephritic test-meal gave a total day urine of 2295 cc and a total night urine of 200 cc. The specific gravities of the various specimens varied from 1020 to 1028.

About 1000 cc of serum was drawn from the right chest on each of four occasions. He grew progressively weaker and died on April 22.

I performed the autopsy four hours after death. There was an extensive old and largely healed tuberculosis in the right upper lobe with much fibrosis and some bronchiectasis. There were a few large tubercles scattered through the rest of the lungs. There were extensive pleural adhesions, a large amount of serum in the right chest, much less in the left.

The heart was entirely normal, weighing 290 gms. There were no other significant lesions except in the kidneys.

The kidneys were very large, 660 gm. together. Capsules free, color light buff mottled with red. Cortical markings gone. Pyramids red in sharp contrast to cortex.

Under the microscope there are patches of new connective tissue all through the cortex, in which the tubes are compressed and the tubular epithelium flat. Outside of these patches the tubular epithelium is swollen and distorted, but rarely desquamated, its cytoplasm takes a universally faint stain and sometimes contains large faintly purplish granules. There is a very extensive exudate

of pus cells throughout the cortex, both in the new connective tissue and in the tubes. There is also an exudate of red cells into the tubes, but these are much fewer in number than the pus cells. Casts and coagulated matter also occur in the tubular lumina. The glomeruli are all profoundly waxy; not only is there not a single normal one, but not one in which the permeability of the loops is not greatly reduced. Most of the glomeruli are of normal size or a trifle large. It is hard to judge of the tuft cells because of the enormous development of amyloid; there is no increase of the capsule cells and no thickening of Bowman's capsule. The arterioles show no sclerosis (Fig. 2).

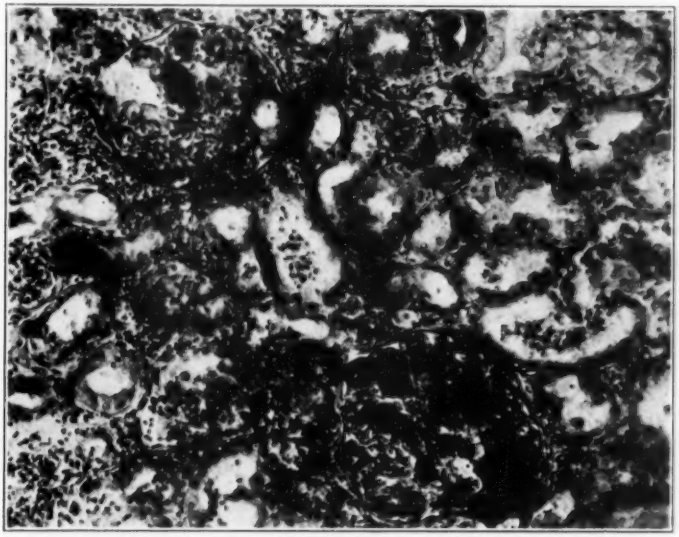

FIG. 2.—Kidney in nephrosis. Note the intense glomerular lesion, the pus in the tubes, the growth of new connective tissue and in some tubes the swollen and faintly staining epithelium. × 133 and reduced.

Here, then, is a case with all the typical symptoms of nephrosis: Anasarca, excessive albuminuria, high specific gravity, no nitrogenous retention, no hypertension, no cardiac hypertrophy, practically normal dye test and test-meal, pallor out of proportion to anemia and watery stools.

The lesions, on the other hand, are definitely inflammatory, for even if one chooses to call the connective tissue a replacement fibrosis, which it does not look like in the sections, the pus exudate is altogether too great to be regarded as incidental, and red cells, which Volhard and Fahr regard as the especial indicators of inflammation, are also exuded. As to the glomeruli, it is all very well to say that amyloid makes no difference in the symptoms. It is

perfectly obvious that such an amyloid change as occurs in these glomeruli must seriously compromise their function by the structural occlusion of their loops alone.

In this case dropsy and albuminuria go hand in hand with extensive degeneration of the tubular epithelium, just as Volhard and Fahr claim, but in all other features the findings run counter to their conception of nephrosis.

Volhard and Fahr believe that sclerosis of the renal arterioles may exist for long periods without any other changes in the kidney, and that hypertension almost invariably accompanies this lesion. They believe this lesion leads to inflammation of other kidney structures and that then a fatal termination presently results. They do not report cases in which death results from hypertension with renal sclerosis the only significant lesion. It is such a case that I have, in conclusion, to report.

CASE III.—*Death with Cardiac Hypertrophy and a Renal Lesion Confined to the Arterioles.* Colored man, aged forty-two years, brought to Roosevelt Hospital moribund January 9, 1922. His wife stated that he had never been sick until four months ago, when he began to have trouble with his heart. This was relieved by digitalis. Three days before admission he was taken with sudden, severe dyspnea and went to bed. He has grown steadily worse.

A huge negro, powerful but not fat; skin moist and cold; marked pulmonary edema. Heart could not be heard; apex in anterior axillary line; pulse too weak to count. Temperature 101.8°, respirations 32. No edema. Blood-pressure 110 systolic. Neither blood nor urine examined. He died a few hours after admission.

The autopsy I did fifteen hours after death. The lungs show marked edema and congestion but no pneumonia. Thyroid gland normal. The heart is enormous, 900 gm. There is massive hypertrophy with enlargement of all chambers. The valves are all normal. Coronaries show a little sclerosis but no stenosis. The heart muscle is normal. Pericardium is normal. The aorta shows very slight atheroma. The kidneys weigh 360 gm. and are about in normal proportion to the size of the body. Their capsules are somewhat adherent; surfaces smooth; cortex and medulla normal on section.

Under the microscope the only striking change is an enormous thickening of nearly every arteriole by the process of ordinary arteritis. The glomeruli all show the dilated loops of chronic congestion and many of them show a little increase of the tuft cells obscuring the individual loop outlines. Rarely the divisions of the tuft are matted or Bowman's capsule a little thickened. These glomerular lesions are secondary or very minor.

There is no formation of new connective tissue. The tubules

are normal in size and contents; their epithelium is somewhat swollen and a little desquamated but shows nothing that may not be easily accounted for by fifteen hours of postmortem deterioration (Fig. 3).

This man, then, apparently died of the failure of an enormously hypertrophied heart. Both the hypertrophy and the failure were presumably caused by a prolonged hypertension, for I believe it is accepted that, when there is no valvular or myocardial lesion, no adherent pericardium and no goiter, cardiac hypertrophy is to be ascribed to hypertension. A blood-pressure of 110 in a patient dying of heart failure with an uncountable pulse, of course, gives no basis for judging his antecedent tension. In such cases every-

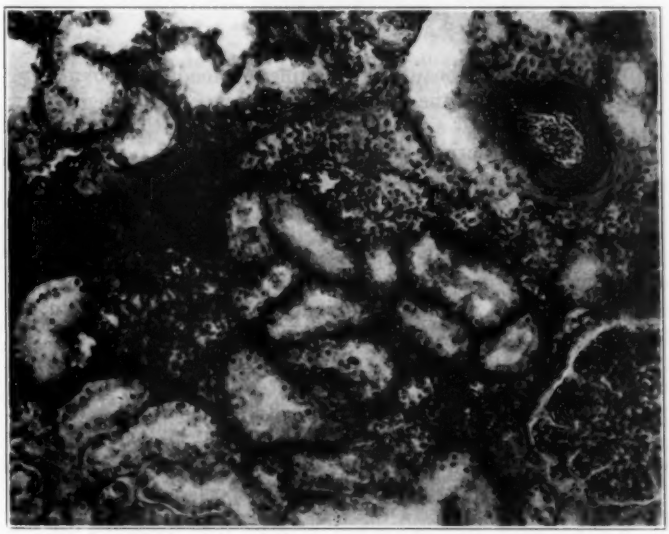

FIG. 3.—Kidney in hypertension. Note the greatly thickened arteriole without other lesions. (× 133 and reduced.)

one looks to a renal lesion for an explanation, and here we find a pronounced renal lesion of peculiar type with no significant pathological changes anywhere else in the body.

It is obvious that, as no one knows what causes increased blood-pressure, any generalizations from such a case are unwarranted. However, as I find myself opposed to Volhard and Fahr's views on nephrosis, so I am much convinced that their work on renal sclerosis is a brilliant contribution and am glad to report a case that strongly supports their contention that there is a close relation between hypertension and vascular renal lesions.

These cases are reported in the belief that as our knowledge of renal function grows it must be correlated as far as possible with changes in structure.

REVIEWS.

THYROID AND THYMUS. By ANDRÉ CROTTI, M.D., F.A.C.S., formerly Professor of Clinical Surgery and Associate Professor of Anatomy, Ohio State University; Surgeon to Grant and Children's Hospitals, Columbus. Imperial octavo. Pp. 774; 105 engravings and 39 colored plates. Half Morocco *de lux*. Philadelphia: Lea & Febiger, 1922.

THIS is the most beautiful example of medical bookmaking which has come from the press in recent years. Binding, paper, type, illustrations and arrangement are all superlative. Opinions may differ as to propriety of issuing in expensive *de lux* form such contributions to medical literature, which are necessarily somewhat ephemeral because of continued progress and knowledge concerning the subject. In defence, it may be said that the book is a joy to the bibliophile, and its comprehensiveness gains for it an expectation of more than ordinary duration of life and usefulness. The book is a happy combination of compilation from the literature and the author's personal views. Whether or not one agrees with the author's opinions, as, for instance, that Graves's disease is a toxic thyroiditis, it is of interest to follow his line of thought, set forth not too dogmatically. The work and opinions of the great masters in this field are freely drawn upon, and due credit given. An excellent balance is maintained between the fundamental, scientific and literary aspects, and the strictly practical considerations. Altogether, this work is the most comprehensive and satisfactory which has yet been issued in single volume on the subject. P.

TEXT-BOOK ON MINOR SURGERY. By JOHN C. VAUGHAN AND ATHEL C. BURNHAM, Director and Visiting Surgeon, Beekman Street Hospital, and Colonel in the United States Army, respectively. Pp. 605; 459 illustrations. Philadelphia and New York: Lea & Febiger, 1922.

IN this work the authors have very clearly portrayed many valuable diagnostic points with their well-chosen illustrations and their descriptions of conditions are also well given. Their outlines of treatment are very good for those who have repeatedly had to

deal with like conditions, and from this standpoint it is not a book for students so much as it is for the dispensary surgeon, industrial surgeon or busy general practitioner.

Many of the subjects are really within the realm of major surgery, but their inclusion makes it a more complete and useful reference book, especially for those coming in contact with emergency surgery.

B.

PREMATURE AND CONGENITALLY DISEASED INFANTS. By JULIUS H. HESS, M.D., Professor and Head of the Division of Pediatrics, University of Illinois, College of Medicine; Chief of Pediatric Staff, Cook County Hospital. Pp. 388; 189 illustrations. Philadelphia and New York: Lea & Febiger, 1922.

THIS book should be of inestimable value to all those concerned with the care of the newborn, for it deals in a capable and comprehensive manner with those two most difficult problems, the bringing to maturity of a premature baby and the diagnosis and proper treatment of the congenitally diseased infant.

The section on the etiology of the premature child should be of much interest to the obstetrician, even though he early delegates the care of infants to the pediatrician, for it is in more thorough prenatal care that the percentage of prematurity will be lowered. The subject of the diet of the premature is considered in accord with the physiology of the immature digestive tract. Wet nursing, maternal feeding and artificial diets are fully discussed. The subject of incubators is handled in detail.

There is nothing to criticize and much to praise in the handling of the subject of general diseases of the newborn, and of the diseases to which the premature infant is particularly prone. Respiratory diseases and syphilis are gone into in detail, with reference to treatment especially. The book closes with a very pertinent chapter on the treatment and care of the premature infant after it has reached extrauterine maturity.

W.

SURGICAL CLINICS OF NORTH AMERICA. Vol. II, No. 5. Southern number. Pp. 326; 126 illustrations. Philadelphia: W. B. Saunders Company, 1922.

IT is an exceedingly difficult undertaking to write a real review of the Surgical Clinics. The multiplicity of writers and subjects makes it almost impossible to touch upon them all. Suffice it to say, however, for the benefit of those who know the magazine,

that this number is up to standard. Among the contributing authors we find representative men from all over the South, men whose names signed to an article guarantee the reader valuable information and enjoyable reading. E.

DIE PHYSIOLOGIE DES KREISLAUFES. Vol III. By ROBERT TIGERSTEDT, Helsingfors, Finland. Second edition. Pp. 320; 134 illustrations. Berlin and Leipzig: Vereinigung Wissenschaftlicher Verleger, 1922.

THE third volume, devoted to the flow of blood in the general circulation, discusses in eight chapters such topics as Torricelli's and Poiseuille's laws, blood viscosity, elasticity of vessel walls, factors changing the flow of blood and blood-pressure in arteries, veins and capillaries. The first two volumes on the movements and the innervation of the heart appeared in 1921, and a fourth volume on the innervation of bloodvessels is expected before the end of 1922. But little comment is needed on the value of this volume as a book of reference—as a text-book for American students it will not have much vogue for obvious reasons. K.

DISEASES OF CHILDREN, MEDICAL AND SURGICAL. By H. T. ASHBY AND C. ROBERTS. Originally by H. ASHBY AND G. A. WRIGHT. Sixth edition. Pp. 769; 202 illustrations. London: Henry Frowde, Hodder & Stoughton.

To the reviewer's knowledge this is the only book which deals both with the medical and surgical diseases of children. Like so many volumes from the pens of our English colleagues, it is well written and does not partake of a too dry or stereotyped style. The subject of pediatrics seems thoroughly covered with thirty-six chapters devoted to physiology, hygiene and diet, diseases of the various systems, scurvy, rickets, metabolisn, radiography and similar topics. In addition there is an appendix describing various diagnostic and therapeutic procedures and formulæ. Without the desire to be unduly critical, several noticeable omissions in the text should be mentioned, especially as the preface contains the usual statement that the book has been brought up to date. In the first place the chapter on feeding is very short and lacking in detail; top milk mixtures are recommended, but one can gain little idea of just how to proceed in feeding the individual infant. Again in the discussion of rickets and spasmophilia no mention is made

of the recent studies of the mineral metabolism, nor is the therapeutic action of light in rickets noted. American pediatrists have become so dependent upon the intraperitoneal administration of fluids in dehydrated conditions, that it is surprising to find that it does not receive recognition in a pediatric text-book. In other respects the text seems as full as the size of the volume warrants. The amount of space allotted to the subjects is well balanced and the important pediatric problems receive due consideration. Taken all in all the book is interesting and useful in a library containing other standard works on pediatrics. M.

TREATMENT OF FRACTURES. By CHARLES L. SCUDDER, M.D., Assistant Professor of Surgery at the Harvard Medical School. Ninth edition, revised, octavo. Pp. 749; 1252 illustrations. Philadelphia: W. B. Saunders Company, 1922.

THIS, the ninth edition, gives to its readers the last word in fractures. The World War gave an enormous impulse to the study of fracture treatment and as a result, many of the old standard ideas have been discarded. The author presents these improvements in the fullest manner possible. Every fracture that the human frame is heir to is discussed fully, and its treatment minutely outlined not only in the written text but by numerous photographs of the deformities as shown on the surface anatomy and by roentgen-ray. An entire chapter is given over to the operative treatment, and other chapters take up the questions of gunshot fractures ambulatory treatment, the roentgen-ray and its relation to fractures, the anatomy of the epiphyses and the use and abuse of plaster-of-Paris dressings. The last chapter deals with a number of dislocations.

The author, in the preface of his work shows clearly that he has aimed at the very latest and best in this line of work. He voices arguments that will make for better and more speedy results in the fracture. E.

ATLAS OF SYPHILIS. By PROF. LEO V. ZUMBUSCH, Munich. Pp. 34; 64 illustrations. New York: William Wood & Co., 1922.

THIS "Atlas of Syphilis" represents a new departure in medical illustration and consists of 64 colored photographs taken direct from patients by color photography. The pictures are true to life, the accuracy of coloration being a remarkable achievement, and form a valuable collection of realistic clinical pictures of the

more common forms of the disease. The 4 illustrations of the spirochæta pallida were taken from water-color drawings and are excellently done. The translation of the work has been prepared by Dr. J. Snowman. The publishers particularly wish to draw the attention to the desirability of using this Atlas in conjunction with a text-book dealing systematically with venereal disease, such as "The Venereal Clinic," by Dr. Clarkson. B.

AN ESSAY ON THE PHYSIOLOGY OF MIND. By FRANCIS X. DERCUM, A.M., PH.D., Professor of Nervous and Mental Diseases, Jefferson Medical College. Pp. 142. Philadelphia: W. B. Saunders Company, 1922.

THE author considers the development of the mind from a biological and biochemical standpoint. He clearly reviews the evolution of the nervous system from the lowest to the highest levels, dealing only with well established facts. With such a basis, he undertakes an explanation of the transmission of impulses in the nerve pathways, leading up to the field of consciousness. Consciousness is defined as from necessity, an ever changing process. The "unconscious mind" he holds to be a contradiction in terms and substitutes "unconscious field" for it. He reiterates his theory expounded in 1895 that hysterical attacks are a result of the retraction of the processes of the neurones, producing in effect an interruption at the synaptic junctions. A brief consideration as an Addendum is given to certain pathological mental states, viewing them from the same biochemical and biological viewpoints. The book is entertainingly written, clear in diction, and easily read. It is of particular value to the neuropsychiatrist for review, and sufficiently free of technicalities to be easily understood by the general practitioner. Even though nothing really new is added to the subject, old concepts and present-day facts are so logically arranged that the sequence is easily followed. It is highly recommended by the reviewer. P.

TEN POSTGRADUATE LECTURES. Pp. 216. New York: William Wood & Co., 1922.

THIS little book contains ten lectures delivered before the Fellowship of Medicine of London. There is a short preface written by Sir Clifford Allbutt in his characteristic delightful style. Among the contributors, one finds such well known authorities as Savage, Hale-White and Rolleston. The lectures deal with divers topics including Morbid Mental Growths (Savage), Prognosis of Exophthalmic Goiter (Hale-White), After-effects of Anesthetics (Mortimer) and Disabilities of the Feet Due to Static or Mechanical

Causes (Trethowan). The lectures are apparently designed to interest general practitioners rather than specialists, and the subjects are discussed in a practical manner. It is hinted that this volume is the first of a series of Fellowship lectures to be issued. If the others conform to the high standard set in the first volume, the project deserves success. W.

A Text-book on Gonorrhea and its Complications. By Georges Luys, M.D., Late Assistant to the Urological Clinique, Hôpital Lariboisière, Paris; Prizeman of the Faculté de Médecine, Paris; Chief Medical Officer of the Urological Center at the Military Hospital, Versailles. Translated and edited by Arthus Foerster, Capt., R.A.M.C., (C.T.), M.R.C.S., L.R.C.P. (Lond.), Late Resident Medical Officer, London Lock Hospital. Third revised edition. Pp. 400; 212 illustrations and 5 colored plates. New York: William Wood & Company, 1922.

The general character of this text-book has not been changed from the first edition which appeared in 1913, the chief features being new chapters which deal with the technic of urethroscopy and urethroscopic treatment. The colored plates of the normal urethra and those depicting the pathological conditions of the urethra due to gonorrhea are particularly good. This book contains twelve chapters. The history of gonorrhea, its etiology, a full description of the gonococcus, the clinical picture of gonorrhea and the symptomatology of this disease are fully described in the early chapters. The numerous complications of gonorrhea are then reviewed and there is a special chapter devoted to gonorrhea in women and children. In the last two chapters there is given a full description of the treatment of acute and of chronic gonorrhea; the methods which have stood the tests and if properly applied, lead to a "certain cure." The book has been illustrated with special care. B.

Diathermie et Diathermotherapie. By H. Bordier. Pp. 490. Paris: Baillière.

This book of about 500 pages presents the subject agreeably and logically. The usual details of currents, their nature and uses, as well as the physiological and chemical effects, are clearly set forth. The mathematics contained can be understood by others than the physicist. In therapeutics the work is the best since Nagelschmidt. The subjects are well worked out from the standpoint of a physician, but would be better for more detailed clinical histories. Some surgeons will surely criticize the claims to benefit chronic appendicitis, salpingitis and anterior poliomyelitis, but the enthusiasm of authorship may surely claim some allowance. C.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Congenital Porphyrinuria Associated with Hydroæstivale and Pink Teeth.—L. MACKEY and A. E. GARROD (*Quart. Jour. Med.*, 1922, **15**, 319) report a remarkable case of congenital porphyrinuria with hydroæstivale, with pink coloration of the milk teeth. The authors have reviewed the literature and find that not more than 15 cases of congenital hematoporphyrinuria have been reported, 10 of which were in males. Hydroæstivale may or may not be associated. The authors' case is unique, in that the teeth of the patient were colored pink. From birth, the patient's mother had noted that the urine had a ruby red color. The first tooth cut had a pink color, and this has been noted in all the teeth of the first dentition. During the period of observation, none of the permanent teeth had been cut. Since it has been shown that there are at least three porphyrins in man, *i. e.*, hematoporphyrin, uroporphyrin and stercoporphyrin, all differing in chemical formula, the author's suggest that the term, hematoporphyrinuria, is a misnomer, as it is not hematoporphyrin which is found in the urine but uroporphyrin. They, therefore, propose that the designation, porphyrinuria, is a more accurate one and should be preferred.

Planorbis Metidjensis as Intermediate Host of Schistosoma Hematobium.—A. BETTENCOURT and I. BORGES (*Compt. rend. Soc. de biol.*, Paris, 1922, **87**, 1039) have made an experimental study, the result of which demonstrates that *Planorbis metidjensis* may serve as an intermediate host for *Schistosoma hematobium*. Mice and guinea-pigs were used as the experimental animals. The hair of the abdomen was shaved, and the animals were then placed in vessels containing water, in which there were many cercariæ derived from *Planorbis metidjensis*. The shape of the vessels was such that the animals had to remain immersed in the water to their necks, thus offering a large surface for the cercariæ to penetrate. The animals were subjected to infestation

during several consecutive or alternate days, and remained in the water each time forty to fifty minutes. Of the mice exposed to infestation, three died. The first had had seven exposures to infestation between May 18 and 25 and died August 2. The second and third were infested after four exposures and died August 16 and 25 respectively. The remaining mice and all the guinea-pigs have survived. Autopsies on the three mice showed adults of *Schistosoma hematobium* in the portal vein, the parasites being already coupled. The ova found were also typical of *S. hematobium*.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.

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Urinary Lithiasis in Children.—THOMAS and TANNER (*Jour. Urol.*, 1922, **8**, 171) says that urinary lithiasis is frequent in childhood and infancy, the average occurrence in the three large series reported being 43 per cent; the average age is seven years. The youngest patient was ten months old. The authors were unable to determine the etiology of urinary stones in infants, although in their opinion infection is one of the factors (21 per cent of the cases). The frequency of involvement of the right kidney to the left is as 21 is to 8. Only 8 per cent were arrested in the ureter. Assuming that the majority of urinary stones in infants (except in the presence of urethral obstruction or malformation) originate in the kidney, 69 per cent will pass into the bladder. The symptomatology in the order of occurrence is as follows: Pain and colic, hematuria, frequency, pyuria, dysuria, nausea and vomiting. The infant ureter is capable of great distention or in some other manner facilitates the easy passage of ureteral stones. Diagnosis depends upon the following positive findings: Roentgen ray, cystoscopy, urinalysis and clinical findings alone (in a minor portion of the cases). Surgery is indicated when stones do not progress through the urinary tract. When stones are bilateral surgery should be carefully considered. Urinary stones in children may remain symptomless for many years.

Tumors of the Testicles.—TARNER (*Surg. Gyn. Obstet.*, 1922, **25**, 565) says that new growths of the testicle occur about once in 2000 male hospital admissions. The disease is practically unilateral, involving both sides only as a metastatic growth from the skin or seminal vesicles. Trauma as an etiological factor in these tumors evidently has some foundation. Practically all cases occur between the ages

of eighteen and fifty years, the period of greatest sexual activity, while either testicle is involved with about equal frequency. Undescended testicles within the canal are more apt to become malignant than normally placed organs. Undescended testicles within the abdomen are relatively immune to malignant changes. In this series, the mortality was about 70 per cent. The so-called mixed type of tumor gives a much higher mortality than the carcinomatous type. Tumors containing cartilage and squamous epithelium seem to have a decidedly unfavorable prognosis.

Treatment of Chronic Empyema Where the Recognized Surgical Procedures Have Failed to Produce Obliteration.—KELLER (*Ann. Surg.*, 1922, **76**, 549) says that the chronic type of empyema, especially those with large cavities should occur but seldom if early aspiration followed by negative pressure treatment is promptly instituted. Empyema cavities can be obliterated by discission and chemical decortication plus implantation of certain muscle bodies. Chemical decortication if used injudiciously may result in rupture of the visceral pleura, dangerous herniation of the lung and hemorrhage. Subperiosteal resection of ribs at the point of division should be discarded and rib section flush with peristeum adopted. Obliteration by expansion of lung which means increased vital capacity should be practised, rather than cavity diminution by collapse of the chest wall. Sterilization of the cavity can often be accomplished, even in long standing cases, but reinfection will invariably occur if the parietal pleura is not removed in a case of over one year's duration, especially if it is of the hemolytic streptococcus variety. Moreover, daily cultures of the wound are necessary to check the progress and to determine the amount of Dakin's solution to be used. The many-step, open or fractional operation, has the following advantages; it permits direct inspection and Dakinization of the entire cavity; it permits the detection and eradication of diverticulæ which are often missed on roentgen-ray examination. It aids in the detection of osteomyelitis and foreign bodies; it insures such immediate improvement in profoundly septic cases that they will permit further operative procedure being carried out with low mortality; it allows the detection and direct closure of bronchial fistulæ; finally the operation can be discontinued at any stage only to be finished later when the patient's condition permits with a mortality far below that of the standard radical operation.

The Pathology and Mechanism of Prostatic Hypertrophy.—TENENBAUM (*Jour. Urol.*, 1922, **8**, 431) says that the progress made in prostatic pathology leads to the conclusion that the so-called prostatic hypertrophy is really a hyperplasia of the periurethral glands. The prostate itself undergoes atrophy through compression, by growth intruding upon it, or primarily as a physiological presenile process occurring in advanced life. Moreover, it cannot be considered a disease. It is with the secondary changes in the urinary tract caused by proliferation of the periurethral glands that the true pathological process develops. The changes in the urethra in regard to size, lumen and curve are the result of various coöperating and antagonistic forces of which the direct pressure of the intruding glands, the indirect influence

of the changes in the bladder upon the urethra and the anatomical peculiarities of the latter are the most important factors. The part of the urethra which is directly subjected to moulding by the growth is the supramontane part of the prostatic urethra. There are two types of intrusion of the growth into the bladder. The direct invasion occurring on or near the sphincter of the bladder which is associated with alterations in the symmetry of the bladder. The indirect raises the floor of the bladder *in toto*, without affecting its symmetry directly. The early stage of bladder involvement is marked by its increased muscular activity while the later stage shows distension and atony combined with impaired muscular activity. The early stages of renal involvement in prostatics are marked by congestion of kidneys with nocturnal polyuria.

Fracture of Tibial Spine.—Blaisdell (*Arch. of Surg.*, 1922, **5**, 560) says that variation in the anatomical constituents of a part must be considered. These affect size, strength and length and are often a part of a peculiar body habitus. Injuries to the knee-joint which may appear slight or trivial, are occasionally accompanied by a crucial triad involvement. Sprain-fracture of knee may be present without giving objective signs. Experiments on the cadaver have demonstrated that force applied over the distal and anterior surface of the thigh driving the femur backward on the tibia when the leg is fixed, will produce rupture of the anterior crucial ligaments and fracture of the tibial spine anteriorly. Inward or outward rotation of the leg may involve an element of the crucial triad, especially when they are accomplished by direct muscular action or mechanical violence.

THERAPEUTICS

UNDER THE CHARGE OF

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AND

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Insulin and Diabetes.—J. J. R. Macleod, (*Brit. Med. Jour.* November 4, 1922) in this "General Statement of the Physiological and Therapeutic Effects of Insulin" summarizes the work that has been going on in his laboratories for some time. As he points out, the diabetes following pancreatectomy has been long ascribed to the absence of a hormone essential for the complete metabolism of sugar. Attempts to isolate this hormone have heretofore been fruitless because the hormone, which has been named insulin (or isletin), is destroyed by the proteolytic ferments also present in the pancreas. Recently

the destruction has been circumvented by tying off the pancreatic duct so that the cells that secrete the digestive enzymes degenerate completely; whereas the isles of Langerhans, which apparently secrete the antidiabetic hormone, remain more or less intact. When extracts of such degenerated glands are injected into dogs rendered diabetic by pancreatectomy, they decrease the hyperglycemia and the glycosuria and cause a great improvement in the general condition of the animal and prolong its life. Active extracts can also be prepared from fetal pancreas, in which proteolytic enzymes have not yet appeared, and from adult ox pancreas by fractional precipitation by alcohol. Insulin preparations are so potent that they must be carefully standardized. For the unit of activity has been selected the amount of insulin which, on subcutaneous injection, lowers the percentage of blood sugar to 0.045 within four hours in a rabbit weighing about 2 kg. and from which food has been withheld for sixteen to twenty-four hours previously. The solution is then concentrated so that 1 cc contains one unit. If the sugar is lowered below 0.045 per cent the animal develops characteristic symptoms consisting of violent convulsions with intervals of coma. These symptoms usually terminate fatally but if the animal is injected subcutaneously with dextrose (1 gm. per kilo), it immediately recovers and usually remains free from symptoms; should the symptoms recur, another injection of dextrose is a successful antidote. The respiratory quotient is a reliable qualitative index of the type of metabolism, having a value of 1 if carbohydrates are the chief foods undergoing katabolism; 0.7 for fats and 0.8 for protein. In diabetes of the severest type, in depancreatized dogs, for example, the respiratory quotient often falls below 0.7 and is not raised by feeding carbohydrates. When diabetic dogs are given insulin along with carbohydrate food, the respiratory quotient immediately rises, showing a restoration of the power to metabolize this class of food; the acetone bodies disappear from the urine and remain absent so long as the administration is continued. In depancreatized dogs, the glycogen content of the liver is very low whereas that of the heart is abnormally high; after insulin and sugar, the per cent of glycogen in the liver rises (to 12 per cent) while that of the heart falls. The fat content of the liver decreases from the abnormally high figure of 12 per cent in untreated animals to below 5 per cent in those treated with insulin and there is, simultaneously, a marked fall in the fat of the blood. These observations indicate that insulin, possibly through its influence on carbohydrate metabolism, also affects that of fat. The hyperglycemia of diabetes disappears and insulin restores the blood sugar to a normal or even subnormal level. All these facts indicate that this new hormone is an essential factor in the regulation of carbohydrate metabolism. Not only does insulin remove the symptoms of diabetes due to the absence of this hormone, but it prevents the development of hyperglycemia (and presumably of glucosuria) which usually follows such procedures as puncture of the floor of the fourth ventricle, the subcutaneous injection of epinephrin, and the various forms of asphyxia, including ether anesthesia. The mode of action of insulin is not yet known. From the fact that insulin causes an increased consumption of sugar by the heart, it appears probable that the site of action is the muscle cell itself, and that it either increases the rate

of combustion of the sugar or hastens its conversion into glycogen. Possessed of all these facts learned from animal experiments, it seemed fair to the author and his co-workers to select cases of human diabetes and try the curative effects of insulin. From all the cases treated the following conclusions seem justified: When insulin is administered subcutaneously in adequate doses, it is capable, within a remarkably short time, of removing the cardinal symptoms of diabetes for a period of several hours. To suppress the symptoms permanently, the injections must be repeated and the practise at present is to give two injections daily. So long as the administration is continued, the patient is able to assimilate much more carbohydrate than previously; he gains in weight and in mental and physical vigor, and the despondency and apathy that are so prominent in these cases disappear. It is in the adolescent forms of the disease that the results have been most marked but there can be little doubt that when insulin comes to be more available, its exhibition, along with intelligent control of diet, will have the same beneficial results in all serious forms of the disease. In cases of threatened coma, insulin is invaluable and the same is true for its use as a precautionary against postoperative risk in surgical practice. Insulin will be put on the market only by licensed manufacturers and not until its usefulness has been fully determined.

Carbon Tetrachloride in the Treatment of Hookworm Disease.—S. M. LAMBERT (*Jour. Am. Med. Assn.*, 1922, **79**, 2055) concludes from his study on more than twenty thousand inhabitants of the Fiji Islands, that carbon tetrachloride is a potent vermifuge and vermicide and is especially effective in the treatment of hookworm disease and less valuable in infection with ascaris, bothriocephalus dispar and oxyuris. Carbon tetrachloride is administered in doses of 0.2 cc per year of age up to fifteen years; the maximal dose thereafter is 3 to 4 cc according to the weight of the patient. After some preliminary tests, the following routine procedure was adopted: the carbon tetrachloride was administered on an empty stomach in the morning and three hours later a dose of magnesium sulphate was given. The carbon tetrachloride is itself a purge but there is less danger of absorption and of systemic action if a saline cathartic is administered after it. No food should be taken for several hours before nor for several hours after the vermifuge. Systemic symptoms include headache, sleepiness, nausea and vomiting and all are prevented or alleviated by the saline purge. The danger of absorption is greatly enhanced if alcohol is taken within several hours of the vermifuge or if the patient is naturally constipated. Reëxamination of the feces of 823 patients indicated that one treatment lowered the infection rate from 100 per cent to less than 9 per cent. Lambert concludes that carbon tetrachloride is well adapted to mass treatment since it is effective, its administration is simple and the cost low (four pence halfpenny per patient).

Respiratory Paralysis Following Quinidine Therapy.—W. D. REID, (*Jour. Am. Med. Assn.*, 1922, **79**, 1974). The author's case of respiratory paralysis is the fifth to be reported in the literature and is the only one which resulted fatally.

PEDIATRICS

UNDER THE CHARGE OF
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The Early Diagnosis of Intussusception.—ZSCHAU (*München. Med. Wchnschr.*, 1922, **69**, 1408) found that intussusception as affecting children particularly was too little appreciated or understood by general practitioners. In a Children's Hospital in Nurnberg there were 19 cases in the period between 1906 and 1921, which was less than 0.1 of 1 per cent of the total admissions. Strong healthy children, many of them breast fed, were suddenly seized with vomiting and severe abdominal pain in paroxysms. After a time diarrhea would develop, and the stools would become bloody. The child would grow continually worse and the facies abdominalis would become marked. The attacks of colic are especially significant. A child that has been quiet will suddenly cry out and writhe in pain. The abdomen becomes flatulent and the intestines become hard. Finally a roller like, only slightly movable, swelling usually above the umbilicus and extending in an oblique direction, can be felt. The temperature is only slightly elevated, the pulse is small and accelerated. Conservative treatment may be tried but Zschau claims that as a rule no result will be experienced. In only 1 of his 19 cases was disinvagination brought about without operation. In 12 of the cases the invagination was ileocolic; in 4 in the colon, and in 2 in the ileum. In 2 cases resection of the intestines was necessary. The earlier the operation was undertaken the less difficult it was. Recovery took place in all but 1 case when the operation was performed within thirty-six hours. The mortality was 30 per cent. The most frequent false diagnosis was dysentery or hemorrhagic enteritis. The false diagnoses were confined mainly to infants in whom there were 4 deaths in 11 cases. Zschau feels convinced that in infants the invagination often is unrecognized, and the cause of death is given as intestinal catarrh. In older children the diagnosis is more accurate probably due to the fact that they can indicate the location of the pain.

Artificial Pneumothorax in Children.—BABONNEIX and DENOYELLE (*Arch. d. med. d. enf.*, 1922, **25**, 599) found in 28 children with progressive pulmonary tuberculosis that the disease was strictly unilateral in 12. Of this number 7 were treated with artificial pneumothorax. In 5 others, pleural adhesions interfered, but in only 2 of these cases had the adhesions been diagnosed. They conclude from their observations that shrinking of the wall on the side of the penumothorax and scoliosis occur early. In 3 cases out of 6, the pneumothorax was followed rapidly by the appearance of a localized pneumonic focus on the opposite side which retrogressed fairly quickly and completely. It seemed to be due to the contamination of the healthy lung by expectoration of bacilli from the diseased lung. To prevent such accidents,

compression should always be slow and progressive so as not to force into the bronchi the contents of the cavity. In 1 case the general condition improved but the bacilli persisted in the sputum. In 3 other cases the local and general results were excellent and seemed possible of being permanent.

A Scarlet Fever Epidemic in an Agricultural School.—DIEHL and SHEPARD (*Jour. Am. Med. Assn.*, 1922, **79**, 2079) describe the observations made by them during this epidemic. This school admits as regular students boys and girls who have completed the eighth grade of public school, and as special students mature men and women. Exclusive of a number of service men who are taking vocational training, most of the students came from rural districts, 59 per cent of them living in places of less than 100 inhabitants. The age period represented was from sixteen to twenty-five, and the individuals had presumably very little immunity to the usual diseases of childhood. At the school 36 per cent of these students lived in dormitories, and 40 per cent took their meals in a common dining room. Most of the others roomed near the campus and took their meals at restaurants or boarding houses. In all 59 cases developed between January 25 and March 26. Of the patients 93.3 per cent were boys and 6.7 per cent were girls; 55.9 per cent lived in rural communities; 33.9 per cent lived in towns of less than 5,000 inhabitants, and 10.2 per cent in cities of more than 5,000 inhabitants. New cases developed at the rate of from 1 in three days to 4 in one day during the epidemic. By means of daily throat inspection with isolation of all suspicious contacts and cases, the epidemic was kept under partial control. It was not until all students with even slightly reddened throats were isolated that new cases failed to develop. From the study of the epidemic, it seems probable that students showing no symptoms other than a moderately reddened throat were responsible for the transmission of much of the infection. A review of the clinical notes in the cases shows a great diversity of symptoms and complications. There were no deaths.

A New Eruptive Fever Associated with Stomatitis and Ophthalmia.—STEVEN and JOHNSON (*Am. Jour. Dis. Child.*, 1922, **24**, 526) have observed 2 cases of a generalized cutaneous eruption not conforming to any recognized dermatological condition. Both cases occurred in boys, one being seven years of age, and the other eight, coming from widely separated sections of New York City with no possibility of contact. Both cases manifested a purulent conjunctivitis, one going on the panophthalmia and total loss of vision, the other responding to treatment, but leaving a severe corneal scar. The pus showed pyogenic organisms, but no gonococci. A high and continuous fever was present in both cases. In the case with loss of vision there was a lobar pneumonia, which may explain the fever. In the other cases the fever was present without other cause than the skin condition. The eruption showed certain characteristics identical in both cases. The onset was with fever, the rash appearing on the back of the neck and chest, spreading to the face, arms and legs during a period of about eighteen days, the last lesions to appear being on the soles of the feet and the palms of the hands. At this time resolution of the first lesions

began. The eruption consisted of oval, dark red to purplish macules, separated by areas of normal skin. These became in a few days raised firm papules of brownish-purple from 0.5 to 2 cm. in diameter, without areola, and without subjective symptoms of pain or itching at any time. A few of the largest spots showed a yellow, dry, necrotic center. The lesions on the forearms and shins were smaller and more thickly together. No pustules or vesicles were to be seen. The scalp was at all times free of lesions, but the mouth and lips were intensely sore and inflamed. In one case bullæ were present in the mouth. After the third week resolution began in the order of the appearance of the lesions. This consisted of the shrinking of the macule to a horny oval of dark brown color with raised papery edges. From the fourth week these scales dropped off, leaving a faint pigmented area; there was no pitting or scarring. By the fifth week the chest, face and back were clear except for the pigmentation, while resolution and crusting were still going on in the arms and legs. Fall of temperature coincided with the period of resolution of the skin lesions. Investigation rules out the possibility of drug rash. In the entire absence of gastro-intestinal symptoms it was not thought to be the rash of food idiosyncrasy. Syphilis was excluded clinically and by laboratory tests. Hemorrhagic measles was the primary diagnosis, but the later course ruled out this possibility. Sepsis with generalized eruption was considered but the superficial nature of the lesions, their character and progressive appearance over three weeks and the leukopenia were the reasons for excluding this diagnosis. Erythema multiforme was also eliminated. The authors feel that this represents a distinct disease which has not been previously recognized.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Precipitation Tests for Syphilis.—The development of precipitation tests for syphilis has resulted in a group of reactions whose clinical standing is, on the whole, distinctly inferior to that of the Wassermann test. The procedures thus far described have in general involved complexities almost as great as those attached to the Wassermann reaction, without a corresponding gain in reliability or sensitiveness. Recently, however, KAHN (*Arch. Dermat. and Syphil.*, 1922, **5**, 570; ibid., 1922, **5**, 734; ibid., 1922, **6**, 332) has devised a precipitation test for syphilis applicable to the blood serum, which is so simple that it may have wide application in the clinical consulting room and the small private laboratory. The method is described in detail in the articles mentioned. The antigen consists of extract of fresh beef heart, one test being performed with a cholesterinized and the other with a noncholesterinized antigen. The antigen is diluted with physio-

logic sodium chloride solution and is best used freshly diluted. The blood serum is obtained by centrifugation and inactivated for one-half hour in the water-bath at 56° C. The diluted antigen and the serum are shaken together and the test read for the spontaneous or strongly positive reactions which take place immediately, the flocculation being visible to the naked eye. The remaining serums are incubated over night at 37.5° C. and read the next morning without shaking. KEIM and WILE (*Jour. Am. Med. Assn.*, 1922, **79**, 870) report the results of a comparison of this test with the Wassermann reaction as carried out in two different standard laboratories in a total of 350 cases. In primary syphilis fifty spontaneous reactions were obtained with agreement between the three tests in 66⅔ per cent. In 33⅓ per cent positive tests were shown by the Kahn reaction, which were negative by the Wassermann. In a treated case the Kahn reaction showed positive in the face of a negative Wassermann. In secondary syphilis the two tests compared favorably in sensitiveness. In osseous late syphilis the Kahn test proved to be less sensitive than the Wassermann with ice-box fixation. In visceral involvement the Kahn test was slightly the more sensitive of the two. In neurosyphilis the two tests compared favorably. In congenital syphilis the Kahn reaction had a slight advantage, and in latent syphilis the Kahn test has a very definite advantage. In the control serums of nonsyphilitic patients, 154 to 157 cases were uniformly negative. The Kahn test showed partial positives as against negative Wassermann reactions in 3 patients with acne, variola and diabetes respectively. Keim and Wile point out the great simplicity of the test, the rapid reading and the visibility of the precipitates and the greater possibilities for standardization in the simplified precipitation test. HERROLD (*Jour. Am. Med. Assn.*, 1922, **79**, 957) has proposed a ring modification of the Kahn test.

Studies in Asymptomatic Neurosyphilis. — J. E. MOORE, (*Johns Hopkins Hosp. Bull.*, 1922, **33**, 231). The author's article is a comprehensive and valuable summary of the experience of the Syphilis Clinic of the Johns Hopkins Hospital in this particular field and gives tangible form to many current clinical impressions. In 352 cases of primary and secondary syphilis, 26.4 per cent were found to have neurosyphilis as detected by neurological examination plus routine spinal puncture after one or two courses of treatment. It is recognized that this probably reduces the percentage of original incidence of this type of involvement. Three groups are recognized, the first presenting only slight pleocytosis, and slight increase in globulin, the second marked pleocytosis and a negative or only mildly positive Wassermann and the third a strongly positive Wassermann with a marked pleocytosis and marked globulin increase. The first group responds to routine continuous treatment; the second to a slight intensification of treatment, and the third requires intraspinal therapy to secure any response. Of the 94 cases presenting neurosyphilitic involvement, 76.6 per cent were asymptomatic and detected only by routine puncture. Of the primary syphilis cases, 29.9 per cent had abnormal fluids, and of the patients with secondary syphilis, 22 per cent. 25 per cent of the cases fell into the first group; 53.1 per cent into the second group, and 23.6 per cent into the third group. The author emphasizes the fact

that the constancy of the percentage of neurosyphilis in early and late cases argues that the fate of a patient with reference to neurosyphilis is decided early in the infection. The optimum time to detect its presence would appear to be by spinal puncture between the twelfth and eighteenth month. An interesting justification of the idea of continuous treatment as compared with lapsing or irregular treatment was found in the fact that three times as many patients who had been irregular in treatment developed neurosyphilis as compared with those whose treatment was regular or continuous. By regular or continuous treatment is meant overlapping courses of arsphenamine and mercury without rest intervals. The author notes that his cases in group two, continue to increase in number with the duration of the infection even during treatment. After reaching 17 per cent it begins to decline again. Patients with strongly positive spinal fluid Wassermanns and high cell counts early in the disease prove resistant and probably constitute the recruiting ground for late neurosyphilis. Negroes were found to present a markedly lower percentage of neurosyphilis than whites. There appears to be some evidence that neurosyphilis tends to appear in an increasing proportion in patients who have mild early cutaneous manifestations. If the blood Wassermann reaction is still positive after a second course of arsphenamine plus all interim mercurialization, a particularly careful search should be made of the osseous, cardiovascular and nervous systems. Of the cases of early neurosyphilis, 21.4 per cent had a resistant blood Wassermann as compared with 8.4 per cent of patients with negative spinal fluids. The author estimates that a systematic intensive continuous treatment should reduce the ultimate incidence of neurosyphilis from between 20 and 30 per cent to approximately 5 per cent. He wisely opposes too much individualization of treatment in early cases urging that it is preferable to treat to a standard which cures the majority rather than to undertreat by an overasymptomatic plan. He suggests that treatment be continued for a full year after the patient has reached complete serological negativity on both the blood and fluid.

The Non-specificity of "Luetin."—Another aspect of the ubiquitous question of non-specificity in the reactions of the body to the *Spirochæta pallida* is the recent demonstration by KOLMER and GREENBAUM (*Jour. Am. Med. Assn.*, 1922, **79**, 2063) of the complete non-specificity of the luetin reaction, and the danger of proceeding to the interpretation of cutaneous tests without properly controlling the non-specific elements and ingredients employed. These authors confirmed the observations of Stokes on the instrumentality of agar in the production of the luetin reaction, and removed the last trace of specificity from the test by showing that the killed *Spirochæta pallida* from pure culture did not produce any reaction when injected into the skins of syphilitics. The reaction is therefore dependent upon secondary factors, such as the medium (ascites agar) upon which the organisms were grown. The worthlessness of much commercial luetin at the present time was recently demonstrated by ALDERSON (*Arch. of Dermat. and Syph.*, 1922, **5**, 610). The great importance of using as controls in cutaneous tests, especially on syphilitics, substances which are capable of engendering the same non-specific reactions as the testing substance, is emphasized.

OBSTETRICS

UNDER THE CHARGE OF

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Tubal Gestation Treated by Salpingotomy. — As a result of careful dissections and study, WHITEHOUSE (*Jour. Obstet. and Gynec. of the Brit. Emp.*, 1922, **29**, 93) has concluded that tubal mole is the direct result of intratubal rupture, and the mole invariably retains a very narrow basis of attachment to the tubal wall, usually on the floor of the tube and always at the proximal end of the mole. When tubal abortion takes place the pedicle of a mole is torn through by peristaltic action of the tube endeavoring to expel the foreign body. Clots may be expelled from the tube through the ostium abdominale without separation of the mole occurring, such clots being frequently ovoid in shape. The conformation of a tubal mole or tubal abortion is the result of pressure of the tubal wall upon the clot, the impression of the normal rugæ being frequently observed. The deciding factor as to whether intra- or extratubal rupture shall occur is the direct outcome of the combination of tissue erosion and tissue tension. This is influenced by the site of the implantation of the ovum in the ampullary, isthmic or interstitial portions of the tube. Evidence, either macroscopic or microscopic, of preëxisting inflammation of the tube appears to be the exception rather than the rule in cases of tubal mole and abortion. The two points upon which the writer would lay special emphasis are: (1) The existence of a pedicle or narrow basis of attachment in all cases, and (2) the ease with which the rest of the mole can, in the case of fresh specimens, be detached from the tubal mucosa. These two points suggested to him the possibility of removing a mole from the tube *in situ* and raised the question as to whether we are justified in sacrificing the tube on all occasions. In a small series of ten cases therefore, previous to removing the tube, he performed salpingotomy and extracted the gestation, which was done without difficulty or hemorrhage either from the pedicle or the tubal wall which was not readily controlled by suture. The tube in these ten cases was then removed and examined in detail for evidence of inflammatory change and in all the specimens the tissues appeared to be normal, and the abnormal implantation of the gestation to be purely accidental in origin. There seemed, therefore, to be quite a good case for salpingotomy and on five subsequent occasions he adopted this method in the treatment of tubal gestation, all of the patients making a normal recovery. Although the writer seems to be quite enthusiastic over this procedure, nevertheless he states that salpingectomy is probably the better procedure, because in the presence of severe hemorrhage life is more important than conservatism, and the interests of the patient are possibly better served by excising rather than suturing a badly lacerated tube. Salpingotomy appears to be worthy of a trial as an alternative pro-

cedure, but time alone will prove whether its adoption is followed by other complications, such as recurrence of the accident, the subsequent development of hydrosalpinx, or the incidence of a tubal chorion-epithelioma.

What is the Present Death Rate in Parturient Women?—This question which is of considerable interest medically and economically receives answer from J. P. GREENHILL (*Surg. Gyn. and Obst.*, 1922, **35**, 614). His statistical material was 10,000 parturient women, among whom occurred 39 deaths, mortality 0.39 per cent. As to the relative mortality of the mother in hospital, among the 39 deaths were 5 delivered by the outpatient service of the hospital in their homes; 1 gave birth before the outpatient physicians could arrive; 1 was delivered by a general practitioner, and 1 by a midwife. There remained 31 deaths in hospital of whom 7 were hospital-ward cases, and 24 were in hospital before under the care of private physicians. This may be understood from the fact that the obstetrical hospital furnishing these statistics is open to the practice of over 300 different physicians. It may represent the practice of the average general physician, but conducted in hospital. In the 39 deaths, what is called general sepsis is charged with 6; peritonitis with 6; shock with 6, the latter divided equally between hemorrhage and rupture of the uterus. There were 5 eclampsias; 4 embolisms; 4 pneumonias; 3 cardiac deaths; 3 toxemic; 3 thrombosis of the vessels of the heart proved by autopsy; 1 status lymphaticus proved by autopsy. The fact that the deaths in hospital are divided among such a number of causes, illustrates the average and probably unavoidable mortality of parturition at the present time. Eight autopsies were obtained, and among the septic cases there were 3 who died before admission to hospital in out-patient service. It is interesting to note that 1 woman died four days after spontaneous birth from a ruptured and infected appendix. Another died after a spontaneous birth from perforation of the small intestine. The 3 deaths from hemorrhage were equally divided among premature separation of the placenta, postpartum hemorrhage and rupture of the uterus. There were 46 cases of eclampsia in the 10,000 with a mortality of 10.9 per cent; 3 patients were said to have toxemia probably without eclampsia; 1 had vaginal hysterotomy, dying on the nineteenth day from embolism; 2 had classic Cæsarean section. The unusual circumstances pertaining in this hospital where over 300 physicians attend patients with hospital advantages make these statistics of unusual interest. The fact that hospital advantages afforded to men of average skill and ability give a low mortality, suggests that further improvement is to be sought in two ways. First by prenatal care, concerning which nothing is said in this report, and second, in making obstetrics a specialty and allotting obstetric cases to obstetricians only.

The Diet Required During Lactation.—HARTWELL (*Lancet*, 1922, **2**, 963) has studied the effects of diet upon warm-blooded animals while nursing their young, to determine the relative quantity of protein and non-protein material needed. If protein matter be given in excess (about 46 per cent of the total solids), the results are bad, and in some

of the lower animals spasms and ultimate death ensue. Fresh cow's milk acts as an antidote to some other proteins, and upon examining milk to determine what it contained which produced this result, there was evidence that vitamin B was the efficient substance. Accordingly, experiments were made with 19 substances commonly used in food. The animals studied were given protein in excess together with butter, lemon juice and salt. To neutralize food of excessive protein content, fruit and vegetable juices were found amply efficient. Best of these were the tomato, potato, carrot and artichoke. Next in efficiency were apple, orange, beet root and vegetable marrow. The juice of cucumbers and juice of grapes had practically no value in the chemistry of food metabolism. Preparations of wheat foods containing yeast and the yolks of eggs were useful. Of all substances fed to nursing animals the yolks of eggs produced the best results upon the offspring. The extracts of beef muscle, cod and herring were useful, and the watery extract of wheat, when it was used in large quantities gave the desired result. Apparently the best of all these substances for neutralizing excess protein in the nursing mothers was the tomato, the active principles of wheat, the yolks of eggs and preparations containing yeast.

GYNECOLOGY

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Complications of Double Kidney.—It is almost an axiom, in reviewing surgical literature, that when one desires to know something about uncommon surgical conditions a reference to the work of the Mayo Clinic will show, as a rule, that the condition is not so uncommon as thought, and, furthermore, the latest thoughts on the subject will usually be presented. For example, BRAASCH and SCHOLL (*Surg., Gynec. and Obst.*, 1922, **35**, 401) state that anomalies in the urinary tract, of themselves, are of no clinical significance. It is only when some pathological complication occurs that their recognition becomes of clinical, as well as of surgical, importance. Pathological, and particularly surgical, complications are prone to develop in the presence of such anomalies, and their clinical discovery is, therefore, comparatively frequent. The most common anomaly in the urinary tract is duplication of the renal pelvis and ureter; such duplication may be unilateral or bilateral, complete or incomplete. When it occurs in a solitary kidney, it is usually termed fused or horseshoe kidney. That duplication is comparatively common is evident from the litera-

ture, although it is doubtful if any other clinic has carefully observed 144 cases of this type, as has been done at the Mayo Clinic. The incidence of aberrant and bilateral duplications of ureters and pelves reported in the literature is too high, owing to the tendency to report the more unusual cases. Of the patients in this series, the duplication was unilateral in 135 (94 per cent) and bilateral in 9 (6 per cent). Of the 135 patients with unilateral duplication, 36 (25 per cent) had complete duplication and 99 (68.7 per cent) had incomplete duplication. Of the 9 patients with bilateral duplications, 8 had complete duplication and 1 had incomplete. Duplication may vary from duplication confined to the renal pelvis to duplicate pelves, with separate ureters opening into the bladder. The pelves are generally unequal in size, the upper being the smaller, and are separated by a bridge of normal renal cortex of variable extent. When an unusually small renal pelvis is outlined in the pyelogram, the possibility of duplication should be suspected. Complete duplication will be discovered more often if a careful search is made routinely for anomaly at the time of cystoscopic inspection. In cases of partial duplication, the diagnosis is made only by means of a pyelo-ureterogram. Hydronephrosis is the most common pathological complication, and is due to ureteral obstruction, generally in the region of the junction of the two ureters in cases of incomplete duplication. In tuberculosis of double kidneys, gross evidence of the disease is generally confined to one segment, usually the lower; but in all cases histological examination reveals tubercles in the intervening renal tissue and extending into the remaining segment. Occasionally, when only one pelvis is outlined by the pyelogram, its unusual shape and contour may be misconstrued with pathological changes occurring in single kidneys, such as atrophic pyelonephritis. Only 61 (42 per cent) of the patients in this series were without pathological complications, and the anomaly was discovered in the examination for other conditions. Fifteen of the 30 patients operated on submitted to primary nephrectomies and 4 to heminephrectomies; 2 of these later required complete nephrectomy. Six pyelolithotomies and 3 ureterolithotomies were performed. In 1 patient hydronephrosis was relieved by the cutting of an aberrant vessel, and in another symptoms were relieved by the ligation of an aberrant ureter from the upper pole of a double kidney. In the treatment of pathological complications in a double kidney, the indication for heminephrectomy is limited to but a few favorable cases, since the remaining half of the resected kidney may become infected and require subsequent removal.

End-results of Surgical Treatment of Cancer of the Cervix.—The enthusiastic acclaim which has greeted the use of radium in the treatment of cancer of the cervix has well nigh put a stop to the operative treatment of this disease in many of the large clinics of this country. Davis (*Ann. Surg.*, 1922, **76**, 395), however, is unwilling to abandon the operative treatment in appropriate cases until more evidence of lasting cures by radium is at hand. The operation which he performs consists of a total abdominal hysterectomy, including a liberal cuff of vaginal wall and wide removal of parametrial tissue. Systematic dissection of the pelvic lymph nodes has not been attempted,

while ligation of the internal iliacs has not proved to be of material advantage, and has been given up since his early cases. In cases presenting a bulky cauliflower outgrowth from the cervix, filling the vault of the vagina, preliminary curettage and cauterization, followed ten days later by radical hysterectomy, have been done. In his series of 32 cases, there have been three operative deaths, an operative mortality of 9.3 per cent, while there has been no mortality in the last 12 cases. These 32 cases were selected out of a series of 85 cases of carcinoma of the cervix applying for treatment, so that his operability rate is 37.6 per cent, although in the latter part of the series the operability rate fell to 33 per cent, in spite of an active publicity campaign carried on in his community. Hysterectomy was undertaken in all cases in which the disease was apparently confined to the cervix, or had invaded the vaginal walls to a limited extent. Mere bulk of the cervical outgrowth into the vagina has not been considered a contraindication, nor has limited parametrial invasion. Actual involvement of the rectal or vesical walls is now considered a contraindication, also massive infiltration of the broad ligaments, as determined by rectal palpation. Mere fixation of the growth in the pelvis has not been found to be a contraindication, as in several cases this has been proved by laparotomy to be due to inflammatory exudate and adhesions. It cannot be denied that there have been distressing complications in those patients who survived the operation. Of the 17 patients who have lived more than five years, there were 4 afflicted with urinary fistulas, although 1 of these closed spontaneously. Postoperative shock was noted in 3 cases, while pyelitis, phlebitis, cystitis and wound sepsis were recorded once each as complications. There were 20 cases operated upon more than five years ago, all of whom have been traced. In 3 cases death occurred as an immediate result of the operation, giving an operative mortality of 15 per cent. In 7 cases the patients are now living and well, while in 1 case the patient died of intercurrent disease without recurrence, seven years after operation. This gives a total of eight five-year cures, or 40 per cent. Recurrence of disease was noted in 9 cases, taking place within one year in 7 cases. The prevalence of urinary fistulas in these cases can be ascribed largely to errors of technic and judgment as the operator was acquiring his early experience. A more conservative selection of cases with substitution of rubber for gauze drainage, avoidance of stripping bare the ureter for considerable distances, and gentleness in its handling, have reduced the incidence of this most distressing sequel in later cases, and yet with all care, ureteral fistula the result of necrosis, remains the great bugbear of the operation, an inherent risk of thorough removal of parametrium.

Ovarian Transplantation.—For many years MARTIN (*Surg., Gynec. and Obst.*, 1922, **35**, 573) has been greatly interested in the subject of ovarian transplantation, and we have quoted him on several previous occasions. His latest contribution to this subject consists of a collective review of the literature, with an extensive bibliography, which will be of great use to those especially interested in this fascinating branch of gynecology. He summarizes his impression of the whole subject by saying that, as more evidence is accumulated from the

literature, the claims of the earlier enthusiasts seem to become less and less substantial. The one most hopeful feature that he is able to glean from the mass of more or less loosely recorded evidence is that the clinical records dealing with transplantation in the human show that, while autotransplants give some evidence of success, homotransplants and heterotransplants give practically none at all. On the other hand, definite evidence of success is recorded as the result of carefully conducted experiments on animals, in which matters of selection of appropriate material and proper technic are more controllable than in dealing with the human. The present status of the question, as may be gleaned from the more recent opinions expressed, is that clinically there is very little to encourage one to believe that transplantation of ovaries, as practised up to the present time, has more than speculative value as a surgical procedure. There is some evidence that autotransplants are of some value in deferring the symptoms of the menopause and delaying the cessation of menstruation. It is difficult, however, not to attribute some of this evidence to suggestive therapeutics or to unattached ovarian tissue left *in situ*. There is practically no convincing evidence that homotransplants or heterotransplants have been successful where the human female has been the recipient, although there is some encouraging evidence recorded in experimental animal surgery that not only autotransplants, but homotransplants and even heterotransplants have been successful, and the sexual function of the castrated animal maintained. The technic followed by the various operators on the human females, in too many instances, seems unsurgical and too often is incompletely and loosely recorded, leaving the impression that the conclusions derived from such work must be unreliable. There is, however, encouraging evidence in all this endeavor to lead one to hope that the subject will be pursued experimentally, especially for the purpose of devising a rational and simple technic, based upon the work of serologists, endocrinologists, hematologists and practical clinical surgeons.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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DIRECTOR OF THE PATHOLOGICAL LABORATORIES, SAO PAULO, BRAZIL.

AND

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A Ten Year Old Strain of Fibroblasts.—EBELING (*Jour. Exp. Med.*, 1922, **35**, 755) described the actual condition of a strain of fibroblasts, obtained from the heart of a chick embryo which had completed the tenth year of its life *in vitro*. At that time the cultures represented

the 1860th generation of the connective-tissue cells. The growth of the tissue fragments was as rapid as during the past years, each fragment generally doubling its volume in forty-eight hours. The cultures had not modified their appearance, many cells dividing mitotically. Although other experimenters believe that cells cultivated *in vitro* did not use the substances contained in the medium and that the masses of tissue did not increase, Ebeling indicated that this was not the case, when the tissues are grown in a medium containing embryonic tissue juices, pointing out that in ten years more than 30,000 cultures had been derived from this fragment of heart less than 1 c.mm. in size and that "If it had been feasible to multiply the tissue to their greatest possible extent, today their mass would be very much larger than the sun," and further, "That the existence of the ten year old strain demonstrates also that the cells are potentially immortal." These experiments have aided in the study of certain biological problems. Pure cultures of cells were found to be as necessary in physiology as pure cultures of bacteria in bacteriology. The cells remained indefinitely young or grew old according to the food material they were given and the extent of the elimination of their catabolic substances. Since it has become possible to obtain strains of lymphyocytes and of epithelial cells living *in vitro* by practically the same procedure that was employed for fibroblasts, the author states that the scope of these studies will be increased.

The Tetanus Bacillus as an Intestinal Saprophyte in Man.—While it is recognized that *B. tetani* is widely distributed in Nature, the role of man as a carrier of this organism has received little attention. It is often stated in the literature that the tetanus bacillus is present in the digestive tract of man, the statement being based, apparently, on the work of Pizzini and also on the fact that this offers the best explanation for some idiopathic cases of tetanus and for those following typhoid fever, dysentery and hemorrhoid operations. TENBROECK and BAUER (*Jour. Exp. Med.*, 1922, **36**, 261) found that 34.7 per cent of 78 male Chinese, save 1, harbored tetanus bacilli in their stools. The organisms were isolated by heating impure cultures to 80° C. for twenty minutes, transferring to sterile bouillon plus tissue in a fermentation tube and plating when the tetanus-like forms predominated. Virtually all the film examinations were made after the tubes had been inoculated four days but latterly it was learned that the tetanus bacilli were more abundant after incubation of five or six days. Field or white mice were inoculated subcutaneously with the centrifugalized branch fluid of the culture tube after incubation of ten days, two receiving 0.001 cc, two 0.01 cc, two 0.01 cc plus approximately 1 unit of tetanus antitoxin, and two 0.1 cc plus the same amount of antitoxin. Only those cultures were called *B. tetani* which produced characteristic spasms and death in mice receiving 0.001 cc and in those mice injected with 0.1 cc plus about 1 unit of tetanus antitoxin in which there were no spasms and the mice survived at least five days. The authors are convinced that tetanus bacillus was growing in the digestive tract, inasmuch as it was present in persons receiving a practically sterile diet for a month or more and because one individual may eliminate several million spores of *B. tetani* in a single stool.

Changes in the Number of Small Lymphocytes of the Blood Following Ligation of the Thoracic Duct.—The extent of appearance of the lymphocyte in the thoracic duct under ordinary conditions or its appearance in the blood stream after splenectomy has been studied by Biedl and von Decastello, after extirpation of important glands by Ehrlich and Rembach, after administration of pilocarpine by Rous and following ligation of the thoracic duct by Davis and Carlson, and Bunting and Huston. During the progress of work on intrathoracic ligation of the thoracic duct in five young adult male cats, LEE (*Jour. Exp. Med.*, 1922, **36**, 247) had an opportunity to observe the effect of ligation of that vessel on the number of small lymphocytes in the blood. The blood for counting was procured from the ear. Differential counts were made by applying Wright's stain to the smears and counting 300 or more cells. It was found that the thoracic duct ligation "produced an immediate decrease in the number of small lymphocytes to the extent of 56 per cent." The preoperative level was again reached at about the end of three weeks. The author believes "that the gradual return of the number of small lymphocytes to the preligation level took place *pari passu* with the establishment of the collateral circulation of the thoracic duct, although," he says "there is no absolute proof of this." It is evident from these observations that the thoracic duct is an avenue for the entrance of at least half of the small lymphocytes to the circulating blood in the cat.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Dermatosis Following the Use of Cutting Oils and Lubricating Compounds.—MCCONNELL (*Public Health Reports*, vol. **37**, No. 29, p. 1773) summarizes a rather exhaustive study of the subject as follows: "In this report attention has been particularly directed toward the practical method of preventing the dermatosis, but it is realized that only a minimum reduction in the number of cases is effected by merely recommending preventives to the workmen without providing adequate sanitary arrangements and employing responsible supervision. The weight of the evidence collected in this investigation incriminates oils and lubricating compounds of all types carrying extraneous matter in suspension as the primary cause in producing the initial dermatosis by mechanical obstruction of the sebaceous orifices, the underlying or basic

cause being a deficiency of the natural oiliness of the skin. Infecting organisms, which usually inhabit the body surface, but which may be carried by cutting liquids, frequently find ingress to the skin through the primary dermatic lesions by reason of the sufferer's scratching the affected surface or by reason of other irritation, and thereby produce a secondary infection of the dermatosis as a complication. In other cases the abrasions produced by particles of the metal become infected and complicate the dermatosis. The condition so arising is not, however, allied to the primary dermatosis, but is similar to conditions, which would be classified under the head of abrasions and infections, such as are commonly found wherever bacteria are present. Prevention depends, first, upon thorough cleanliness, and, second, upon the application of lanolin or lanolin and castor oil to the skin at the beginning of the work period. Cure is accomplished by rest of the affected parts and by constant use of the preventive measures."

Influenza: Framingham Epidemic and Postepidemic Observations.—Studies conducted under the FRAMINGHAM COMMUNITY HEALTH AND TUBERCULOSIS DEMONSTRATION (*Framingham Monograph*, 1922, No. 9) led to the following conclusions: (1) A very small percentage (1 per cent) of the group have had a recurrent attack of influenza subsequent to the primary epidemic. (2) A fairly large percentage seemed to have acquired the practice of going to their own physician for an examination, either as a result of the general medical examination propaganda, or partly as a result of the emphasis given to this idea in connection with the postepidemic activities. Twenty-nine per cent of the individuals canvassed in the second follow-up stated that they had been to their own physician at least once during the preceding six months for medical advice, other than for specific medical treatment. (3) Cardiac signs seem to have been moderately stirred up by the epidemic, the percentage of cases, as compared with preëpidemic examinations, increasing from 5 to 8 per cent in the first follow-up. However, the disappearance of these symptoms in the second follow-up seems to have been substantial, and the general wave of cardiac symptoms seems to have subsided to a figure approximately the same as the preëpidemic finding. (4) Persistent, vague and undiagnosed respiratory findings were increased by the epidemic, this increase apparently persisting during the second and third follow-ups. (5) While the number of active cases of tuberculosis discovered in the group after the epidemic in the first follow-up was increased by 1 per cent over the preëpidemic findings, this apparent lighting up of the disease seems to have been more than compensated for by the rearrest of the active process in this group, as indicated both by the findings in the second and third follow-ups (0.3 per cent in the second follow-up) and by the general observations of the medical staff, leading to the conclusion that the epidemic has not been a conspicuous, responsible factor in increasing the prevalence of active tuberculosis. The conclusion is further substantiated by the mortality-rates in Framingham and, indeed, throughout the United States.

Analysis of 123 Cases of Anthrax in the Pennsylvania Leather Industry.—SMYTH and BRICKER (*Jour. Indust. Hyg.*, 1922, **4**, 53) report

123 cases of anthrax connected with the tanning industry in the twelve years from 1910 to 1921, inclusive. This number represents almost 12 per cent of the directly exposed employees. The mortality among these 123 cases was over 21 per cent. The authors state that in the five-year period for which accurate statistics were made, there was a yearly morbidity rate of almost 2 per cent of the directly exposed employees. The directly exposed employees include those handling raw stock and those soaking and liming this stock. Anthrax has been contracted from the handling of non-packer cattle hides from Texas, Mexico, China, India and South America, and from goat skins from many regions. Anthrax has been contracted from the handling of both dry and wet salted hides and skins, and from both certified and uncertified stock, and anthrax bacilli have been isolated from both. The present practice of certification offers little or no protection to the tanner. The mortality of cases treated in hospitals has been considerably less than one-half that of unhospitalized cases. In Pennsylvania apparently the best results of treatment have been obtained by the injection of strong phenol solutions (25 to 50 per cent) locally around the area of the initial lesion, with or without excision of the lesion. The use of antianthrax serum with excision of the local lesion has also given excellent results, and the authors do not desire to create the impression that it should not be used. They state they would be inclined, from a consideration of the Pennsylvania experience, to advocate the continued intensive use of a reliable serum subcutaneously or intravenously, combined with excision of the local lesion and the injection of concentrated phenol solution around the wound. Early diagnosis, prompt hospitalization if possible, and absolute rest are essential for success in any form of treatment. Anthrax continues to be a decided menace to both the cattle hide and goat skin tanner and will continue to be so until some method is developed whereby tanneries cease to receive anthrax infested raw stock. Seymour-Jones advocates for England the prohibition of the importation of any raw stock not previously converted to the wet salt state by means of his formic acid and mercuric chloride method. Whatever method may be finally adopted the authors feel strongly that all undisinfected imported stock should be disinfected at one or more centrally located government disinfecting stations before being shipped to the tanners, as the English government is doing at present with wool and hair.

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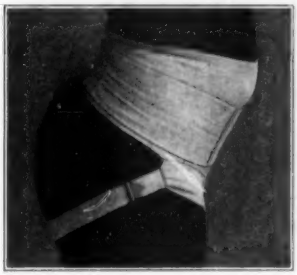

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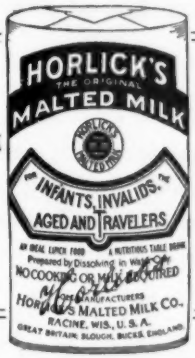
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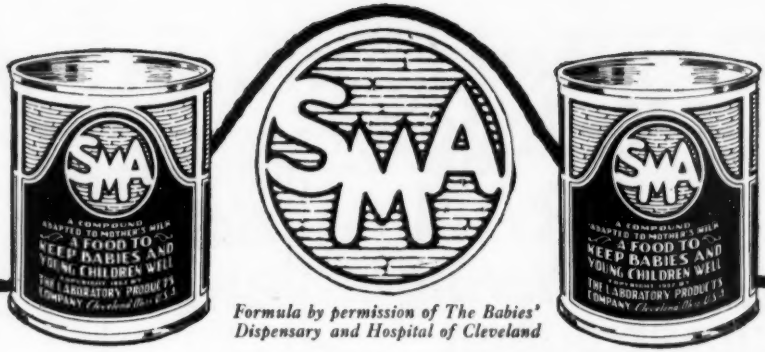
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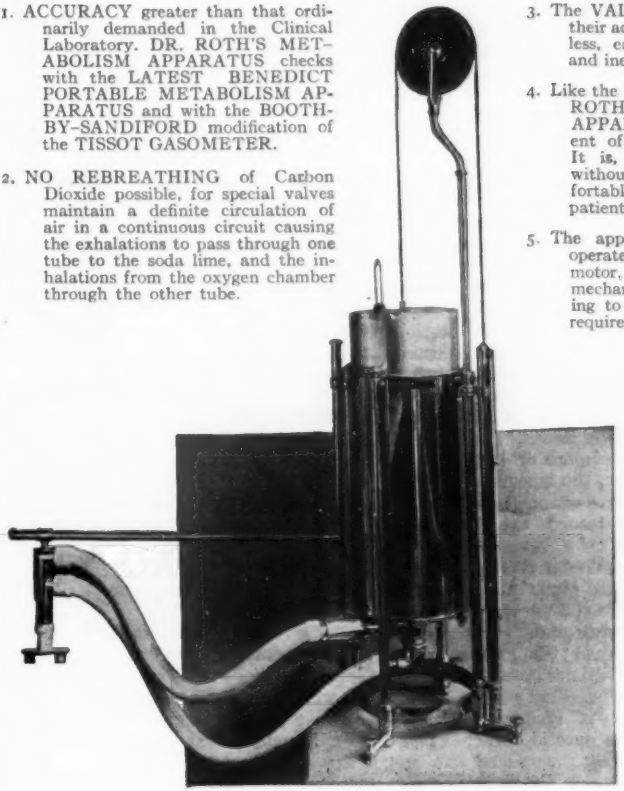

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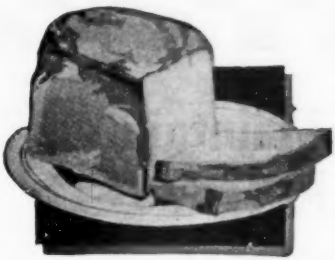

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